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Specification

A CCR4 antagonist and medicinal applications thereof.

The Field of Technology

This invention relates to the following, namely, a compound having CCR4 antagonism useful as pharmaceutical, a process for the production and applications thereof.

Background Technique

The chemokine has been known as an endogenous, basic protein having leukocyte chemotaxis / activating action and showing strong binding to heparin. Presently, it is considered that not only does chemokine controll infiltration of specific leukocyte during inflammation / immunoreaction, but also it isinvolved in homing of lymphocyte under the physiological condition, migration of hemocyte precursor cell and somatic cell.

As for hemocytes, th differentiation, proliferation and cell death thereof are controlled by various kinds of cytokines. Inflammation is locally observed in vivo, and differentiation, maturation or the like of lymphocyte take place in specific locations. In other words, various kinds of necessary cells accumulate to a specific site by migration, and thereby a series of inflammation / immunoreaction is caused. Accordingly, in addition to differentiation, proliferation and death of cells, the migration of cells is an indispensable phenomenon for immune system.

The migration of hemocytic cells in-vivo firstly begins with the transition from the hematopoiesis originated in AGM region during development process to permanent hematopoiesis in bone marrow via fetus liver. Furthermore, precursor cell of T cells / thymus dendritic cells migrates from fetus liver / bone marrow to thymus, and cell differentiation occurs in thymus environment. The T cells which received clone selection move to secondary lymphoid tissue and is participated in immunoreaction at the periphery. The Langerhans cells of the skin that ahs captured antigen and is activated / differentiated, migrate to T cell region of local lymph node, and activate naive T cells as dendrite cells. Memory T cells home in again to lymph node via lymph duct / blood vessel. Moreover, B cells, T cells in intestinal epithelium, gamma delta T cells, NKT cells and dendritic cells are migrated and differentiated from bone marrow without passing through thymus, and they are participated in immune reaction.

Chemokine is deeply involved in such migration of various kinds of cells. For example, CCR4 which is a receptor of MDC, TARC is expressed on Th2 cells (cf; J. Immunol. 161, 5111 (1998)),

and it is known to play an important role in swarming of Th2 cells to the site where, immunity / inflammatory reaction relating Th2 cells is induced. In mouse OVA-induced respiratory tract hypersensitivity model, anti-MDC antibody inhibited the number of eosinophils accumulating to lung interstitium, and inhibited respiratory tract hypersensitivity (cf; J, Immunol, 163, 403 (1999)). In mouse OVA-induced respiratory tract hypersensitivity model, anti-TARC antibody inhibited respiratory tract hypersensitivity and at the same time, inhibited invasion of eosinophils and lymphocytes to the respiratory tract (cf; J. lmmunol., 166, 2055 (2001)). In the investigation using Nc/Nga mouse, the rise of TARC quantity and MDC quantity was observed in atopic dermatitis-like lesions (cf; J. Clin. Invest., 104, 1097 (1999)). As for the participation of CCR4 in pathosis of human, CCR4-positive memory T lymphocyte count in peripheral blood was increased corresponding to severity of dermatitis in atopic dermatitis patients (cf; J. Allergy Clin. lmmunol., 107, 353 (2001)), and TARC quantity in serum also showed correlation to severity. (cf; J. Allergy Clin. lmmunol., 107, 535 (2001)). The quantity of TARC in serum and induced expectoration was increased in asthma patients (cf; Allergy, 57, 173 (2002)). MDC concentration in blood was high in Th2 diseases such as atopic dermatitis, Sezary's syndrome or the like (cf; Eur. J. lmmunol. 30, 201 (2000)).

There are many reports suggesting the relevance to inflammatory diseases other than allergic diseases, and CCR4-positive cells were found to be selectively accumulated in the affected part of lupus nephritis (cf; Arthritis Rheum, 46, 735 (2002)). Expression of TARC and MDC was elevted in the affected part of Crohn disease (cf; Eur. Cytokine Netw., 12, 468 (2001)). The CCR4 expression was elevated in peripheral blood CD4-positive cells of systemic erythematosus patients compared with healthy person (cf; J. Leuko. Biol. 70, 749 (2001)).

Moreover, chemokine is known to fulfill various role in immunoreaction apart from the migration of various kinds of cells. In investigation using CCR4 deficient mouse, the fatality case rate due to high dose LPS shock was lowered compared with wild type, and furthermore, decreases in the quantity of TNF alpha, IL-1 beta and MIP-1 alpha in blood after LPS administration were confirmed. Moreover, in rat fulminant hepatic failure model (P.acnes+LPS), anti-TARC antibody inhibited the rise of ALT quantity in blood and the rise of expression of TNF alpha and FasL in liver, and furthermore, improved the fatality rate in rats (cf; J. Clin. Invest., 102, 1933 (1998)). It was shown that CCR4 contributed to the binding of activated T cells and dendritic cells (cf; J. lmmunol., 167, 4791 (2001)). Furthermore, the fact that TARC and MDC cause platelet aggregation via CCR4 (cf; Thrombosis Research, 101, 279 (2001)) is one of diversity of physiological activities of these chemokines and chemokine receptors.

In this way, chemokine and chemokine receptors are greatly participated in regulation of inflammation / immunoreaction through the mechanism wherein chemokine receptor is expressed in various kinds of specific cells at specific period and the effector cells thereof accumulate to the site where chemokine is produced.

From the above, because CCR4 antagonist has TNF alpha control action and function inhibitory action of effector cells in addition to CCR4 antagonism, the use is considered as preventative and/or therapeutic agent with respect to Inflammation / allergic disease [for example, systemic inflammatory reaction syndrome (SIRS), anaphylaxis or anaphylactoid-reaction, allergic vasculitis, transplantation organ rejection, hepatitis, nephritis, nephropathy, pancreatitis, rhinitis, arthritis, inflammatory eye disease (for example conjunctivitis or the like), inflammatory enteric disease (for example ulcerative colitis, Crohn disease, easinophilic gastroenteropathy or the like) cerebro- circulatory organ system diseases (for example arteriosclerosis, thrombosis, ischemic / repefusion disorder, restenosis, infarction or the like), respiratory system disease (for example, acute respiration distress syndrome [ARDS], asthma, allergic bronchopulmonary aspergillosis or the like), dermatosis (for example dermatitis (for example atopic dermatitis, psoriasis, contact dermatitis, eczema, urticaria, pruritus or the like), or the like), autoimmune disease (for example, multiple sclerosis, chronic rheumatism, systemic lupus erythematosus, type I diabetes mellitus, glomerulonephritis, Sjogren syndrome or the like)], metabolism / endocrine system diseases [for example diabetes mellituses], cancerous disease [for example malignant neoplasm (for example, leukemia, cancer, metastatic cancer or the like), or the like], infection [for example viral disease (for example acquired immunodeficiency syndrome, SARS or the like) or the like].

On the other hand, there is description to the effect that the compound represented by general formula (X)

$$J^X - M^X \qquad (X)$$

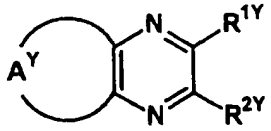
(wherein, JX represents aromatic ring moiety, and MX represents G protein coupling receptor interaction moiety) can bind to G protein coupling receptor. As example compounds, compounds represented by general formula (X-1)

$$A^X - L^{1X} - B^X - L^{2X} - E^X \qquad (X\text{-}1)$$

(wherein, AX represents optionally substituted alkyl, aryl, heteroaryl and the like, and L1X represents O, S, CHOH, O(CH2)nX, and nX represents 0, 1, 2 or 3, and BX represents optionally substituted 5-7 membered aromatic ring which may contain 0-3 heteroatoms, and L2X represents CH2C=O, NHC=O, OC=O or the like, and EX denotes G protein coupling receptor interaction moiety. Wherein the definition of each symbol is a partial extraction) are described to bind to G

protein coupling receptor (cf; for example, WO00/46203).

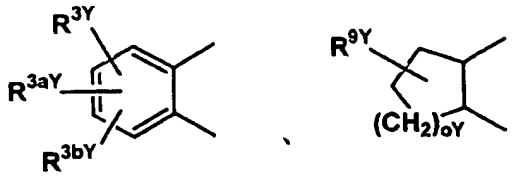
Moreover, tehre is a description to the effect that the the compound represented by general formula (Y)



(Y)

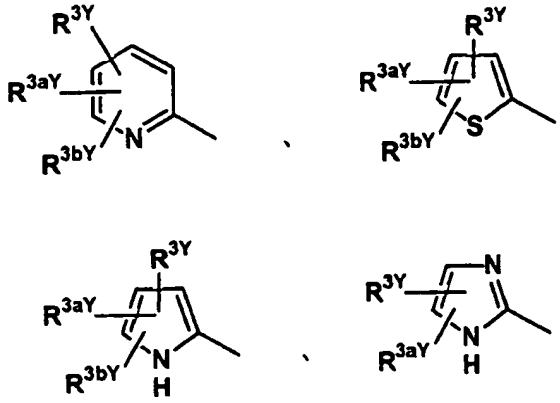
is useful as IL-8 receptor (CXCRI and CXCR2) agonist (cf. for example WO99/42463).

(wherein, AY represents,

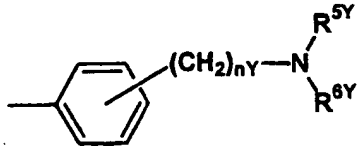


or the like, and R3Y, R3aY and R3bY each independently represent hydrogen, alkyl and the like, and oY denotes 1 or 2, and R9Y represents hydrogen, alkyl, and

R1Y represents alkoxy, halogen,



and R2Y represents CF3, -NR10YR11Y, or the like, and R10Y represents hydrogen, alkyl, aralkyl, and R11Y represents



and nY represents 0 or 1,

R5Y and R6Y each independently denote hydrogen, alkyl, cycloalkyl and the like. Wherein, Wherein the definition of each symbol is a partial extraction).

Moreover, to date, several compounds are reported as low molecular weight compound having

CCR4 antagonism (cf. for example, WO02/30357, WO02/30358 and WO02/94264).

However, pyrazine derivatives having CCR4 antagonism has not beed reported at all to date.

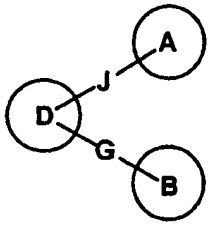
Disclosure of the Invention

The development of compound useful as prevention and/or therapeutic agent of asthma, atopic dermatitis or the like, or as a drug, and having safe CCR4 antagonism and excellent oral absorbability is desired earnestly.

These inventors carried out assiduous investigations in order to discover the compounds having CCR4 antagonism, and as a result, discovered that the the compounds of this invention represented by general formula (I) fulfilled the purpose. This invention was completed as a result of this.

Namely, this invention comprises the following:

1. A compound or salts thereof represented by general formula (I)



(I)

(in the formula ring A, ring B and ring D each independently denote optionally substituted cyclic group, and J denotes a bond or a spacer having the number of main chain atoms of 1-8, and G represents a bond or a spacer having the number of main chain atoms of 1-4),

2. A compound in accordance with aforesaid 1, wherein

is

(wherein, DJ and DG each independently denote carbon atom or nitrogen atom,

---- denotes single bond or double bond, and

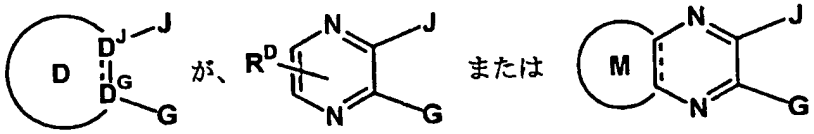
when ---- denotes double bond, DJ and DG represent carbon atom),

3. A compound in accordance with the aforesaid 2, wherein the ring D is an optionally substituted carbocyclic ring,

4. A compound in accordance with the aforesaid 2, wherein the ring D is an optionally substituted heterocyclic ring,

5. A compound in accordance with the aforesaid 4, wherein the heterocyclic ring is 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms,

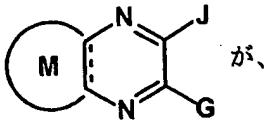
6. A compound in accordance with the aforesaid 2, wherein



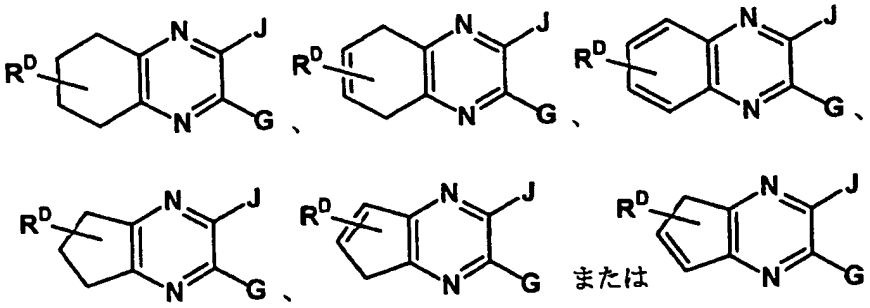
is or

(wherein, RD denotes substituent of ring D, and M represents 3-11-membered optionally substituted monocyclic or bicyclic group),

7. A compound in accordance with the aforesaid 6, wherein



is



or

(wherein, RD has the same said meaning as described in aforesaid 6),

8. A compound in accordance with aforesaid 1, wherein the ring A is an optionally substituted carbocyclic ring,

9. A compound in accordance with aforesaid 1, wherein the ring A is an optionally substituted heterocyclic ring,

10. A compound in accordance with aforesaid 8, wherein the carbocyclic ring is C3-15 mono-, di- or tri-cyclic carbocyclic ring,

11. A compound in accordance with aforesaid 9, wherein the heterocyclic ring is 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms,

12. A compound in accordance with aforesaid 10, wherein the carbocyclic ring is benzene ring or naphthalene ring,

13. A compound in accordance with aforesaid 11, wherein the heterocycle is pyridine ring, pyrazole ring, dioxan indan ring or benzodioxan ring,

14. A compound in accordance with aforesaid 1, wherein the ring B is an optionally substituted carbocyclic ring,

15. A compound in accordance with aforesaid 1, wherein the ring B is an optionally substituted heterocyclic ring,

16. A compound in accordance with aforesaid 14, wherein the carbocyclic ring is C3-15 mono-, di- or tri-cyclic carbocyclic ring,

17. A compound in accordance with aforesaid 15, wherein the heterocyclic ring is mono-, di- or tri-cyclic heterocycle of 3-15-membered containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom,

18. A compound in accordance with aforesaid 16, wherein the carbocyclic ring is C3-8monocyclic carbocyclic ring,

19. A compound in accordance with aforesaid 17, wherein the heterocyclic ring is 3-8-membered monocyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom,

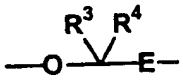
20. A compound in accordance with aforesaid 18, wherein the carbocyclic ring is benzene ring,

21. A compound in accordance with aforesaid 19, wherein the heterocyclic ring is pyridine ring or thiophene ring,

22. A compound in accordance with aforesaid 1, wherein J is a spacer having the number of main chain atoms of 1-8 containing at least one oxygen atom,

23. A compound in accordance with aforesaid 22, wherein the oxygen atom is bonded to ring D,

24. A compound in accordance with aforesaid 22, wherein J is



(in this group, R3 and R4 each independently denote hydrogen atom or C1-8 alkyl group, and E represents bond or a spacer having the number of main chain atoms of 1-6),

25. A compound in accordance with aforesaid 24, wherein R3 and R4 each independently represent hydrogen atom or methyl group.,

26. A compound in accordance with aforesaid 24, wherein E is a bond,

27. A compound in accordance with aforesaid 24, wherein E is a spacer having the number of main chain atoms of 1-6,

28. A compound in accordance with aforesaid 27, wherein E is C1-4 alkylene group or C1-3 alkylene oxy group,

29. A compound in accordance with aforesaid 28, wherein E is methylene group or methylene oxy group,

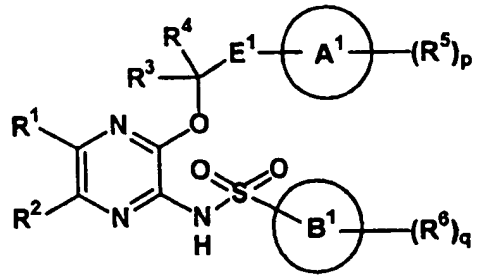
30. A compound in accordance with aforesaid 1, wherein G is a spacer having the number of main chain atoms of 1-4 containing at least one nitrogen atom,

31. A compound in accordance with aforesaid 30, wherein G is -NRT1-, -NRT1-SO2-, -NRT1-CO-, -NRT1-CO-NRT2-, -NRT1-SO2-NRT2-, -NRT1-COO-, NRT1-O-, -NRT1-NRT2-, -NRT1-W-, -SO2-NRT1-, -CO-NRT1-, -OCO-NRT1-, -CO-NRT1- or -W-NRT1- (in the groups, W denotes an optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-3, and RTI and RT2 each independently represent hydrogen atom, optionally substituted C1-8 alkyl

group, optionally substituted C2-8 alkenyl group, optionally substituted C2-8 alkynyl group or optionally substituted 3-8-membered cyclic group),

32. A compound in accordance with aforesaid 31, wherein G is -NH-SO2-,

33. A compound in accordance with aforesaid 1, wherein the compound is general formula (A)



(A)

(in the formula, R1 and R2 each independently represent (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) halogen atom, (6) cyano group, (7) nitro group, (8) -CONR7R8, (9) -COOR9, (10) Cyc1 or (11) C1-8 alkyl group substituted by 1-5 groups arbitrarily selected from (a) -CONR7R8, (b) -COOR9, (c) -OR10, (d) -NR11R12, (e) halogen atom and (f) Cyc1, or

R1 and R2 may be linked together to forn C3-4 alkylene group, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH_2-CH_2- are denoted. Wherein the formed carbon ring may be substituted by C1-8 alkyl group, C2-8 alkenyl group, C2-8 alkynyl group, C1-8 alkoxy group, halogen atom, cyano group, nitro group, hydroxy group (in this group, R7 and R8 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc2, (6) -OR13, (7) C1-8 alkyl group C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 groups arbitrarily selected from (a) -OR13, (b) -NR14R15, (c) -NR16COR17, (d) halogen atom, (e) CF3 and (f) Cyc2, or

R7 and R8 may be linked together with the nitrogen atom that they are bonded to forn a 3-8-membered monocyclic heterocycle containing at least 1 nitrogen atom and also containing as other heteroatoms 0-3 nitrogen atoms, 0-1 oxygen atom and/or 0-1 sulfur atom. Wherein aforesaid heterocycle may be substituted by C1-8 alkyl group substituted by (a) C1-8 alkyl group, (b) halogen atom, (c) hydroxy group or (d) hydroxy group,

R13-R17 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc1 or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by Cyc1,

R9-R12 each independently denote (1) hydrogen atom (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group (5) Cyc1 or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by Cyc1,

Cyc1 denotes mono-, di- or tri-cyclic carbocyclic of C3-15 or 3-15-membered mono-, di- or tri-cyclic heterocycle of containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as or heteroatoms. Wherein Cyc1 may be substituted by 1-5 species of R18,

R18 denotes (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) trifluoromethyl group, (8) trifluoromethoxy group (9) -OR19, (10) -SR20, (11) -NR21R22, (12) -COR23, (13) -COOR24, (14) -NR25COR26, (15)-CONR27R28, (16) Cyc2 or (17) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by1-5 groups arbitrarily selected from (a) halogen atom, (b) cyano group, (c) nitro group, (d) trifluoromethyl group, (e) trifluoromethoxy group (f) -OR19, (g) -SR20, (h) -NR21R22, (I) -COR23, (j) -COOR24, (k) -NR25COR26, (l) -CONR27R28 and (m) Cyc2,

R19-R28 each independentlydenote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc2, or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by Cyc2,

Cyc2 denotes monocyclic carbocyclic of C3-8 or 3-8-membered monocyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms. Wherein Cyc2 may be substituted by 1-5 species of R29, and

R29 denotes (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) hydroxy group, (8) trifluoromethyl group, (9) trifluoromethoxy group or (10) -OR100, and

R100 represents C1-8 alkyl group),

R3 and R4 each independently denote hydrogen atom or C1-8 alkyl group,

E1 denotes a bond or C1-6 alkylene group. Wherein the carbon atoms of said alkylene group may be substituted by oxygen atom, sulfur atom or NR30-,

R30 denotes (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) phenyl group, or (5) C1-8 alkyl group substituted by phenyl group,

ring A1 denotes mono-, di- or tri-cyclic carbocyclic of C3-15 or 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms,

R5 denotes (1) C1-8 alkyl group (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) trifluoromethyl group, (8) trifluoromethoxy group, (9) -OR31, (10) -NR32R33, (11) -NR34COR35, (12) Cyc3 or (13) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 groups arbitrarily selected from (a) halogen atom, (b) cyano group, (c) nitro group, (d) trifluoromethyl group, (e) trifluoromethoxy group, (f) -OR31, (g) -NR32R33, (h) -NR34COR35, and (i) Cyc3,

R31-R35 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc3 or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8

alkynyl group substituted by 1-5 groups arbitrarily selected from (a) Cyc3, (b) -OR36 and (c) -NR37R38,

R36-R38 each independently denotes (1) hydrogen atom, (2) C1-8 alkyl group, (3) -OR39 or (4) -NR40R41,

R39-R41 each independently denotes a hydrogen atom or C1-8 alkyl group,

Cyc3 denotes monocyclic carbocyclic of C3-8 or 3-8-membered monocyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom,

ring B1 denotes mono-, di- or tri-cyclic carbocyclic of C3-15 or 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms,

R6 is (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) trifluoromethyl group, (8) trifluoromethoxy group, (9) -OR42, (10) -NR43R44, (11) -SR101, (12) -SO2R102, (13) -COR103, (14) -COOR104, (15) Cyc2 or (16) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 group arbitrarily selected from (a) -COOR104, (b) -NR105COR106 and (c) Cyc2,

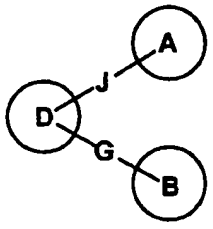
R42-R44, R101-R106 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) Cyc2, (4) -COR 107 or (5) C1-8 alkyl group substituted by 1-5 halogen atoms,

R107 denotes C1-8 alkyl group, and

p and q each independently denote 0 or an integer of 1-5.],

34. A prodrug of compound in accordance with aforesaid 1,

35. A medicinal composition which is obtained by containing the compounds or salts thereof represented by general formula (I)



(I)

(in the formula ring A, ring B and ring D each independently denote optionally substituted cyclic group, and J denotes a bond or a spacer having the number of main chain atoms of 1-8, and G represents a bond or a spacer having the number of main chain atoms of 1-4),

36. A medicinal composition in accordance with aforesaid 35 that is a chemokine receptor antagonist,

37. A medicinal composition in accordance with aforesaid 36, wherein the chemokine receptor is CCR4,

38. A medicinal composition in accordance with aforesaid 37 that is a prevention and/or therapeutic agent of CCR4-mediated disease,

39. A medicinal composition in accordance with aforesaid 38, wherein the CCR4-mediated disease is inflammation / allergic disease, metabolism / endocrine system disease, cancerous disease or infection,

40. A medicinal composition in accordance with aforesaid 39, wherein the CCR4-mediated disease is inflammation / allergic disease,

41. A medicinal composition in accordance with aforesaid 40, wherein the inflammation / allergic disease is respiratory system disease or dermatosis,

42. A medicinal composition in accordance with aforesaid 41, wherein the respiratory system disease is asthma,

43. A medicinal composition in accordance with aforesaid 41, wherein the dermatosis is atopic dermatitis,

44. A prevention and/or therapy method of CCR4-mediated disease in mammalian organisms characterised in that an effective dose of compounds or salts thereof in accordance with aforesaid 1 is administered to mammalian organism,

45. Use of compounds or salts thereof in accordance with aforesaid 1 to produce prevention and/or therapeutic agent of CCR4-mediated disease,

46. A medicinal composition formed from a prevention and/or therapeutic agent of CCR4-mediated disease containing compounds or salts thereof in accordance with aforesaid 1 as effective component, and one or more drugs selected from bronchodilator, steroid drug, non-steroid anti-inflammatory agent, leukotriene receptor antagonist, phosphodiesterase inhibitor, immunosuppressive drug, antiallergic drug, mediator releaser suppressant antihistamine, metabolism promotion agent and/or chemokine inhibitor,

47. A medicinal composition in accordance with aforesaid 35 that is a function inhibitor of effector cell,

48. A medicinal composition in accordance with aforesaid 47 that is a cell migration function inhibitor,

49. A medicinal compositions in accordance with aforesaid 35 that is TNF alpha controlling agent.

In this specification, as "cyclic group" in "optionally substituted cyclic group" represented by ring A, ring B and ring D, for example carbocyclic ring or heterocyclic ring and the like are nominated.

As carbocyclic ring, for example "mono-, di- or tri-cyclic carbocyclic ring of C3-15" is nominated. Wherein, to "mono-, di- or tri-cyclic carbocyclic ring of C3-15", mono-, di- or tri-cyclic unsaturated carbon ring of C3-15, partially or completely saturated carbocyclic ring, spiro bonded bicyclic carbocyclic and crosslinked bicyclic carbocyclic are included.

As " mono-, di- or tri-cyclic unsaturated carbon ring of C3-15, partially or completely saturated carbocyclic ", for example cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclo tri dodecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cyclo heptene, cyclooctene, cyclopentadiene, cyclohexa diene, cyclohepta diene, cyclo octadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, bi phenylene, as-indacene, s-indacene, acenaphthylene, acenaphthene, fluorene, phenalene, phenanthrene, anthracene ring and the like are proposed. As the "spiro bonded bicyclic carbocyclic", for example, spiro[4.4] nonane, spiro[4.5] decane, spiro[5.5] undecane ring and the like are proposed, and as "crosslinked bicyclic carbocyclic", for example, bicyclo[2.2.1] heptane, bicyclo[2.2.1] hepta-2-en, bicyclo[3.1.1] heptane, bicyclo[3.1.1] hepta-2-en, bicyclo[3.2.1] octane, bicyclo[2.2.2] octane, bicyclo[2.2.2] oct-2-en, adamantane, noradamantane ring and the like are nominated. Among these, as "mono-, di- or tri-cyclic aromatic carbon ring of C3-15", for example, benzene, azulene, naphthalene, phenanthrene, anthracene ring and the like are nominated.

As heterocycle, for example "mono-, di- or tri-cyclic heterocyclic of a member of 3-15 including

1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom" and the like is nominated. Wherein, in "mono-, di- or tri-cyclic heterocyclic of a member of 3-15 including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom", mono-, di- or tri-cyclic heterocyclic of a member of 3-15 including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom, heterocycle in which a part or all thereof is saturated, spiro bonded bicyclic heterocycle and crosslinked bicyclic heterocycle are included.

As "mono-, di- or tri-cyclic heterocyclic of a member of 3-15 including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom, heterocycle in which a part or all thereof is saturated" for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyrane, oxepine, thiophene, thiopyrane, thiepine, oxazole, isoxazole, thiazole, iso thiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, iso indole, indolizine, benzofuran, isobenzofuran, benzothiophene, iso benzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzo oxazole, benzothiazole, benzimidazole, chromene, benzo oxepine, benzo oxazepine, benzo oxadiazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzoazepine, benzodiazepine, benzofurazan, benzothiadiazole, benzotriazole, carbazole, beta-carborine, acridine, phenazine, dibenzofuran, xanthene, dibenzothiophene, phenothiazine, phenoxazine, phenoxathiine, thianthrene, phenanthridine, phenanthroline, perimidine, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperadine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydro oxepine, tetrahydro oxepine, perhydro oxepine, thiirane, thiethane, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydro oxazole, tetrahydro oxazole (oxazolidine), dihydroiso oxazole, tetrahydroiso oxazole (iso oxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazane, tetrahydrofurazane, dihydro oxadiazole, tetrahydro oxadiazole (oxadiazoline), dihydro oxazine, tetrahydro oxazine, dihydro oxadiazine, tetrahydro oxadiazine, dihydro oxazepin, tetrahydro oxazepin, perhydro oxazepin, dihydro oxadiazepin, tetrahydro oxadiazepin, perhydro oxadiazepin, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine,

tetrahydrothiadiazine, dihydrothiazepin, tetrahydrothiazepin, perhydrothiazepin, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathian, dihydrobenzo oxazine, dihydrobenzo thiazine, pyrazino morpholine, dihydrobenzo oxazole, perhydrobenzo oxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dihydrobenzo azepin, tetrahydrobenzo azepin, dihydrobenzodiazepine, tetrahydrobenzodiazepine, benzodioxepan, dihydrobenzo oxazepine, tetrahydrobenzo oxazepine, dihydrocarbazole, tetrahydrocarbazole, perhydrocarbazole, dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, perhydrodibenzofuran, perhydrodibenzothiophene, dioxolane, dioxane, dithiolane, dithiane, dioxan indan, benzodioxan, chroman, benzodithiolane, benzodithiane, 6,7-dihydro-5H-cyclopenta [b] pyrazine, 5H-cyclopenta [b] pyrazine, imidazo [2,.1-b][1,3] thiazole ring and the like are proposed. As the "spiro bonded bicyclic heterocycle", for example, azaspiro[4.4] nonane, oxazaspiro[4.4] nonane, dioxaspiro[4.4] nonane, azaspiro[4.5] decane, thiaspiro[4.5] decane, dithiaspiro[4.5] decane, dioxaspiro[4.5] decane, oxazaspiro[4.5] decane, azaspiro[5.5] undecane, oxaspiro[5.5] undecane, dioxaspiro[5.5] undecane ring and the like are proposed. As "crosslinked bicyclic heterocycle", for example, azabicyclo[2.2-1] heptane, oxabicyclo[2.2.1] heptane, azabicyclo[3.1.1] heptane, azabicyclo[3.2.11 octane, oxabicyclo[3.2.1] octane, azabicyclo[2.2.2] octane, diazabicyclo[2.2.2] octane ring and the like are nominated.

Among these, as "3-15 membered mono-, di- or tri-cyclic heteroaromatic ring including 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom", for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, iso thiazole, furazan, oxadiazole, thiadiazole, indole, iso indole, benzofuran, isobenzofuran, benzothiophene, iso benzothiophene, indazole, quinoline, isoquinoline, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzo oxazole, benzothiazole, benzimidazole, benzofurazan, benzothiadiazole, benzotriazole, carbazole, beta-carboline, acridine, phenazine, dibenzofuran, dibenzothiophene, phenanthridine,

phenanthroline, perimidine ring and the like are nominated.

The "substituent" is substituent, it is not restricted in particular in "option ally substituted cyclic group" represented with ring A and ring B. As aforesaid "substituent", for example substituent and the like below to exemplify is nominated.

As "substituent" in aforesaid "option ally substituted cyclic group", for example (1) substituent selected from following primary group, (2) substituent selected from following secondary group, (3) optionally substituted 3-15 membered cyclic group, (4) optionally substituted carbamoyl group, (5) optionally substituted aliphatic hydrocarbon group and the like are proposed, and these arbitrary substituents of 1-10, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be substituted.

The first group

(1) halogen atom (chlorine, bromine, fluorine, iodine), (2) cyano group, (3) nitro group, (4) trifluoromethyl group, (5) trifluoromethoxy group, (6) oxo group, (7) thioxo group

The second group

(1) -ORal group, (2) –NRa1Ra2 group, (3) –NRa1CORa2 group, (4) –COORa1 group, (5) –SRa1 group, (6) -SORa1 group, (7) -SO2Ra1 group, (8) –CORa1 group (in this group, Ra1, Ra2 independently denote (a) hydrogen atom, (b) optionally substituted aliphatic hydrocarbon group or (c) optionally substituted 3-15 membered cyclic group. Moreover, when plural of substituents are selected from this group, plural of Ra1 or plural of Ra2 may be the same or different respectivelly.)

Wherein, as "aliphatic hydrocarbon group" in "optionally substituted aliphatic hydrocarbon group" represented by Ral, Ra2, for example "branched or straight chain aliphatic hydrocarbon group" and the like are nominated. As "branched or straight chain aliphatic hydrocarbon group", for example "aliphatic hydrocarbon group of carbon number 1-8" is nominated, and as "aliphatic hydrocarbon group of carbon number 1-8", for example C1-8 alkyl group, C2-8 alkenyl group, C2-8 alkynyl group and the like are nominated.

As C1-8 alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl group and isomeric groups thereof and the like are nominated.

As C2-8 alkenyl group, for example, vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl,

octenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, hexatrienyl, heptatrienyl, octatrienyl group and isomeric groups thereof and the like are nominated.

As C2-8 alkynyl group, for example, ethinyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, butadiynyl, pentadiynyl, hexadiynyl, heptadiynyl, octadiynyl, hexatriynyl, heptatriynyl, octatriynyl group and isomeric groups thereof and the like are nominated.

As "substituent" in "optionally substituted aliphatic hydrocarbon group" represented by Ra1, Ra2, for example, (1) substituent selected from aforesaid primary group, (2) substituent selected from the following tertiary group, (3) optionally substituted 3-15 membered cyclic group and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be substituted.

The third group

(1) –ORb1 group, (2) –NRb1Rb2 group

(in the group, hydrogen atom, Rb1 and Rb2 independently denote (a) hydrogen atom, (b) hydroxy group, (c) amino group, (d) C1-8 alkyl group (the same aforesaid meanings), (e) C1-8 alkoxy group (for example methoxy, ethoxy, propoxy, butoxy, penthyloxy, hexyloxy, heptyloxy, octhyloxy group and isomeric group thereof) (f) mono- or di-substituted C1-8 alkylamino group (for example methylamino, ethylamino, propylamino, dimethylamino, diethylamino group and the like), (g) C1-8 alkyl group substituted with "mono- or di-substituted C1-8 alkylamino group" (C1-8 alkyl denotes the same aforesaid meaning), (h) C1-8 alkoxy group substituted with "mono- or di-substituted C1-8 alkylamino group" (C1-8 alkoxy denotes the same aforesaid meaning). Moreover, when plural of substituents are selected from this group, plural of Rb1 or plural of Rb2 may be the same or different respectivelly).

In this specification, as "3-15 membered cyclic group", in "optionally substituted 3-15 membered cyclic group" for example, aforesaid "C3-15 mono-, di- or tri-cyclic carbocyclic", "3-15 membered mono-, di- or tri-cyclic heterocyclic including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom" and the like are nominated.

As "substituent" in "optionally substituted 3-15 membered cyclic group", for example, (1) substituent selected from aforesaid primary group, (2) optionally substituted aliphatic hydrocarbon group, (3) substituent selected from the following quarternary group (4) optionally substituted 3-8 membered cyclic group and the like are proposed, and these arbitrary substituents of 1-10, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be

substituted. Wherein, as "aliphatic hydrocarbon group" in "optionally substituted aliphatic hydrocarbon group", for example aforesaid "aliphatic hydrocarbon group of carbon number 1-8" or the like is nominated. As "substituent" in "optionally substituted aliphatic hydrocarbon group", for example, (1) substituent selected from aforesaid primary group, (2) substituent selected from the following quarternary group, (3) optionally substituted 3-8 membered cyclic group and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

The fourth group

(1) –ORc1 group, (2) –SRc1 group, (3) –NRc1Rc2 group, (4) –CORc1 group, (5) –COORc1 group, (6) –NRc1CORc2 group, (7) –CONRc1Rc2 group, (8) –SORc1 group, (9) -SO2Rc1 group (in this group, Rc1, Rc2 independently denote (a) hydrogen atom, (b) 3-8 membered cyclic group which may have substituent or (c) aliphatic hydrocarbon group which may be substituted by 3-8 membered cyclic group which may have substituent. Moreover, when plural of substituents are selected from this group, plural of Rb1 or plural of Rb2 may be the same or different respectivelly).

Wherein as "aliphatic hydrocarbon group" in "aliphatic hydrocarbon group which may be substituted by 3-8 membered cyclic group which may have substituent" represented by Rc1, Rc2, for example aforesaid "aliphatic hydrocarbon group of carbon number 1-8" or the like is nominated.

In this specification, as "3-8 membered cyclic group" in "optionally substituted 3-8 membered cyclic group", for example "C3-8 monocyclic carbocycle", "3-8 membered monocyclic heterocycle" and the like are nominated. Wherein, "C3-8 monocyclic carbocycle" include C3-8 monocyclic unsaturated carbon ring, carbocyclic ring in which a part or all is saturated.

As "C3-8 monocyclic unsaturated carbon ring, carbocyclic ring in which a part or all is saturated", for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexa diene, cyclohepta diene, cyclo octadiene, benzene ring and the like are nominated. Among these, as "C3-8 monocyclic aromatic carbon ring", for example benzene ring and the like are nominated.

Moreover, as "3-8 membered monocyclic heterocycle", for example "3-8 membered monocyclic heterocycle including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom" and the like is nominated. Wherein, as "3-8 membered monocyclic heterocycle

including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom", 3-8 membered monocyclic heterocycle including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom, heterocycle in which a part or all is saturated are included.

As "3-8 membered monocyclic heterocycle including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom, heterocycle in which a part or all is saturated are included", for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyrane, oxepine, thiophene, thiopyrane, thiepine, oxazole, isoxazole, thiazole, iso thiazole, furazane, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazolin, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazin, tetrahydropyridazine, perhydropyridazine, dihydroazepin, tetrahydroazepin, perhydroazepin, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydro-furan, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thiirane, thiethane, dihydro-thiophene, tetrahydrothiophene, dihydrothio pyran, tetrahydrothio pyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydro-oxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (iso oxazolidine), dihydrothiazol, tetrahydrothiazole (thiazolidine), dihydroiso thiazole, tetrahydroiso thiazole (isothiazolidine), dihydrofurazane, tetrahydrofurazane, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane ring and the like are nominated. Among these, as "3-8 membered monocyclic heteroaromatic ring including 1-4 nitrogen atom, 1-2 oxygen atom and/or 1-2 sulfur atom as heteroatom", for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, thiadiazole ring and the like are nominated.

As "substituent" in "optionally substituted 3-8 membered cyclic group", for example, (1) substituent selected from aforesaid primary group, (2) C1-8 alkyl group (it has the same aforesaid

meaning), (3) C2-8 alkenyl group (it has the same aforesaid meaning), (4) C2-8 alkynyl group (it has the same aforesaid meaning), (5) hydroxy group and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

As "optionally substituted carbamoyl group" as "substituent" in "optionally substituted cyclic group" represented by ring A and ring B, other than the unsubstituted carbamoyl group, N-mono substituted carbamoyl group and N,N-disubstituted carbamoyl group are nominated. "N-mono substituted carbamoyl group" denotes carbamoyl group containing one substituent on nitrogen atom, and "N,N-disubstituted carbamoyl group" means carbamoyl group containing two substituents on nitrogen atom. As substituent of carbamoyl group, for example, (1) aforesaid "optionally substituted 3-15 membered cyclic group", (2) optionally substituted aliphatic hydrocarbon group, (3) hydroxy group which may be protected and the like area proposed, and these may be substituted 1-2 in the substitutable position. Moreover, substituent of carbamoyl group in "N,N-disubstituted carbamoyl group" may be formed (4) optionally substituted 3-8 membered nitrogen containing heterocycle together with the nitrogen atom that they are bonded.

Wherein, as "hydroxy group which may be protected", protected hydroxy group is nominated other than hydroxy group. As "protecting group" in "protected hydroxy group", for example, (1) optionally substituted C1-8 alkyl group (C1-8 alkyl group has the same aforesaid meaning), (2) optionally substituted C2-8 alkenyl group (C2-8 alkenyl group has the same aforesaid meaning), (3) optionally substituted C2-8 alkynyl group (C2-8 alkynyl group has the same aforesaid meaning), (4) aforesaid "optionally substituted 3-15 membered cyclic group" and the like are proposed, wherein as "substituent" in "optionally substituted C1-8 alkyl group", "optionally substituted C2-8 alkenyl group", "optionally substituted C2-8 alkynyl group", for example, (1) aforesaid "optionally substituted 3-15 membered cyclic group", (2) substituent selected from aforesaid primary group and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

Moreover, as "aliphatic hydrocarbon group" in "optionally substituted aliphatic hydrocarbon group" as substituent of "N-mono substituted carbamoyl group" and "N,N-disubstituted carbamoyl group", for example aforesaid "aliphatic hydrocarbon group of carbon number 1-8" and the like is nominated. Wherein, as "substituent" in "optionally substituted aliphatic hydrocarbon group", for example, (1) aforesaid substituent selected from primary group, (2) aforesaid "optionally substituted 3-15 membered cyclic group", (3) aforesaid substituent selected from the secondary group and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

In this specification, as "3-8 membered nitrogen containing heterocycle" in "optionally substituted 3-8 membered nitrogen containing heterocycle", for example "3-8 membered monocyclic heterocyclic including as at least one nitrogen atom as heteroatom and 0-3 nitrogen atom, 0-1 oxygen atom and 0-1 sulfur atom as other heteroatom" and the like is nominated. Wherein, "3-8 membered monocyclic heterocyclic including as at least one nitrogen atom as heteroatom and 0-3 nitrogen atom, 0-1 oxygen atom and/or 0-1 sulfur atom as other heteroatom" includes 3-8 membered monocyclic unsaturated heterocyclic including as at least one nitrogen atom as heteroatom and 0-3 nitrogen atom, 0-1 oxygen atom and/or 0-1 sulfur atom as other heteroatom, heterocyclic ring in which part or all thereof is saturated. As "3-8 membered monocyclic unsaturated heterocyclic including as at least one nitrogen atom as heteroatom and 0-3 nitrogen atom, 0-1 oxygen atom and/or 0-1 sulfur atom as other heteroatom, heterocyclic ring in which part or all thereof is saturated", for example pyrrole, imidazole, triazole, tetrazole, pyrazole, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, tri azoline, tri azolidine, tetrazolin, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazin, tetrahydropyridazine, perhydropyridazine, dihydroazepin, tetrahydroazepin, perhydroazepin, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, dihydro-oxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (iso oxazolidine), dihydrothiazol, tetrahydrothiazole (thiazolidine), dihydroiso thiazole, tetrahydroiso thiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine ring and the like are nominated. Among these, as "3-8 membered monocyclic heteroaromatic ring heterocyclic including as at least one nitrogen atom as heteroatom and 0-3 nitrogen atom, 0-1 oxygen atom and/or 0-1 sulfur atom as other heteroatom", for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, iso thiazole, furazan, oxadiazole, thiadiazole ring and the like are nominated.

Wherein, as "substituent" in "optionally substituted 3-8 membered nitrogen containing heterocycle", for example, (1) substituent selected from aforesaid primary group, (2) hydroxy

group, (3) C1-8 alkyl group which may be substituted by 1-8 hydroxy group (C1-8 alkyl group has the same aforesaid meaning) and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

As "aliphatic hydrocarbon group" in "optionally substituted aliphatic hydrocarbon group" as "substituent" in "optionally substituted cyclic group" represented by ring A and ring B, for example aforesaid "aliphatic hydrocarbon group of carbon number 1-8" and the like are nominated. Wherein, as "substituent" in "optionally substituted aliphatic hydrocarbon group", for example, (1) substituent selected from aforesaid primary group, (2) aforesaid "optionally substituted 3-15 membered cyclic group", (3) aforesaid "optionally substituted carbamoyl group", (4) aforesaid substituent selected from secondary group and the like are proposed, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

As"substituent" in "optionally substituted cyclic group" represented by ring D, it is not restricted in particular so long as it is substituent. As "substituent", for example substituent represented by RD and the like is nominated.

As "substituent of ring D" represented by RD, for example, substituent exemplified as "substituent" in "optionally substituted cyclic group" represented by aforesaid ring A and ring B and the like is proposed, and these arbitrary substituents of 1-10, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be substituted.

The "spacer having number of main chain atoms of 1-4" represented by G means the interval of main chain atoms which are connected by 1-4. Wherein, "number of main chain atoms" is counted so that the main chain atoms become minimum. For example, the number of atoms of 1,2-cyclopentylene is counted as 2, the number of atoms of 1,3-cyclopentylene is counted as 3.

As "Spacer of atomic number 1-4 of main chain", for example divalent group having a series of 1-4 main chain atoms arbitrarily selected from for example -O-, -S-, -CO-, -SO-, -SO2-, optionally substituted nitrogen atom, optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4, optionally substituted divalent 3-8 membered monocyclic carbocyclic group and optionally substituted divalent 3-8 membered monocyclic heterocyclic group and the like are nominated. Wherein, as "optionally substituted nitrogen atom", in addition of -NH-, hydrogen atom in "-NH-" group is arbitrary substituted to (1) optionally substituted C1-8 alkyl group (C1-8 alkyl group has the same aforesaid meaning), (2) optionally substituted C2-8 alkenyl

group (C2-8 alkenyl group has the same aforesaid meaning), (3) optionally substituted C2-8 alkynyl group (C2-8 alkynyl group has the same aforesaid meaning), (4) aforesaid "optionally substituted 3-8 membered cyclic groups" is denoted. Wherein, as "substituent" in "optionally substituted C1-8 alkyl group", "optionally substituted C2-8 alkenyl group", "optionally substituted C2-8 alkynyl group" as "substituent" in "optionally substituted nitrogen atom", for example, (a) hydroxy group, (b) aforesaid "optionally substituted 3-8 membered cyclic group" and the like are nominated, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

As "divalent aliphatic hydrocarbon group of carbon number 1-4" in "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4", for example C1-4 alkylene group (for example –CH2-, -(CH2)2-, -(CH2)3-, -(CH2)4- and the like), C2-4 alkenylene group (for example –CH=CH-, -CH2-CH=CH-, -CH=CH-CH2-, -(CH2)2-CH=CH-, -CH=CH-(CH2)2-, -CH2-CH=CH-CH2- and the like), C2-4 alkynylene group (for example –C≡C-, -CH2-C≡C-, -C≡C-CH2-, -(CH2)2-C≡C-, -C≡C-(CH2)2-, -CH2-C≡C-CH2- and the like) and the like are nominated. Moreover, as "substituent" in "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4", for example , (1) C1-8 alkyl group (the same aforesaid meaning), (2) C1-8 alkoxy group (the same aforesaid meaning), (3) halogen atom (the same aforesaid meaning), (4) hydroxy group, (5) oxo group, (6) thioxo group, (7) amino group, and (8) =N-ORn group (in the group, Rn denotes hydrogen atom or the same meaning as "substituent" in aforesaid "optionally substituted nitrogen atom") and the like are proposed, and these arbitrary substituents of 1-5, preferably 1-2 species may be substituted at positions that can be substituted.

Moreover, as "divalent 3-8 membered monocyclic carbocyclic group" in "optionally substituted divalent 3-8 membered monocyclic carbocyclic group", for example divalent group formed from ring exemplified as aforesaid "C3-8 monocyclic carbocyclic" by eliminating arbitrary two hydrogen atoms and the like is nominated. As "substituent" in "optionally substituted divalent 3-8 membered monocyclic carbocyclic group", for example groups exemplified as "substituent" in aforesaid "optionally substituted 3-8 membered cyclic group" and the like is nominated, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

As "divalent 3-8 membered monocyclic heterocyclic group" in "optionally substituted divalent 3-8 membered monocyclic heterocyclic group", for example divalent group formed from ring exemplified as aforesaid "C3-8 monocyclic heterocyclic" by eliminating arbitrary two hydrogen atoms and the like is nominated. As "substituent" in "optionally substituted divalent 3-8

membered monocyclic heterocyclic group", for example groups exemplified as "substituent" in aforesaid "optionally substituted 3-8 membered cyclic group" and the like is nominated, and these arbitrary substituents of 1-8, preferably 1-5 species may be substituted at positions that can be substituted.

As "spacer having number of main chain atoms of 1-4" including at least one nitrogen atom", it denotes the divalent group including one or more aforesaid "optionally substituted nitrogen atom" in group among aforesaid "spacer having number of main chain atoms of 1-4", and when "optionally substituted nitrogen atom" is included two or more, substituent of each nitrogen atom may be the same or different. As "spacer having number of main chain atoms of 1-4" including at least one nitrogen atom", for example preferably, -NRT1-, -NRT1-SO2-, -NRT1-CO-, -NRT1-CO-NRT2-, -NRT1-SO-NRT2-, -NRT1-COO-, -NRT1-O-, -NRT1-NRT2-, -NRT1-W-, -SO2-NRT1-, -CO-NRT1-, -OCO-NRT1-, -O-NRT1-, -W-NRT1- (in this group, W denotes "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-3 " and RT1 and RT2 independently denotes hydrogen atom or the same meaning as substituent in aforesaid "optionally substituted nitrogen atom") and the like are nominated.

Wherein, as "divalent aliphatic hydrocarbon group of carbon number 1-3" in "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-3", among the group exemplified as aforesaid "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4", C1-3 alkylene group (for example –CH2-, -(CH2)2-, -(CH2)3- and the like), C2-3 alkenylene group (for example –CH=CH-, -CH2-CH=CH-, -CH=CH-CH2- and the like), C2-3 alkynylene group (for example –C≡C-, -CH2-C≡C-, -C≡C-CH2- and the like) are shown. Moreover, "substituent" in "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-3" has the same meaning as "substituent" in aforesaid "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4".

The "spacer having the number of main chain atoms of 1-8" represented by J means that interval of the atoms of main chain which are connnected by 1-8. Wherein, the "number of of main chain atoms" is counted in the same way as in the "spacer having the number of main chain atoms of 1-4" so that the atoms of the main chain becomes minimum. For example, the number of atoms of 1,4-phenylene is counted as 4, and the the number of atoms of 1,3-phenylene is counted as 3.

As "spacer having the number of main chain atoms of 1-8", a divalent group having a series of 1-8 main chain atoms arbitrarily selected from for example -O-, -S-, -CO-, -SO-, -SO2-, aforesaid "optionally substituted nitrogen atom", optionally substituted divalent aliphatic hydrocarbon

group of carbon number 1-8, aforesaid "3-8-memebred optionally substituted divalent monocyclic carbocyclic group" and aforesaid "3-8-memebred optionally substituted divalent monocyclic heterocyclic group", and the like are nominated.

Wherein, as "divalent aliphatic hydrocarbon group of carbon number 1-8" of the "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-8", for example C1-8 alkylene group (for example methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene or the like), C2-8 alkenylene group (for example ethenylene, propenylene, butenylene, butadienylene, pentenylene, pentadienylene, hexenylene, hexadienylene, heptenylene, heptadienylene, octenylene, octadienylene or the like), C2-8 alkynylene group (for example ethylnylene, propynylene, butynylene, butadiynylene, pentynylene, pentadiynylene, hexynylene, headiynylene, heptynylene, heptadiynylene, poctynylene, ocadiynylene or the like) and the like are nominated. Moreover, as "substituent" of aforesaid "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-8", for example, species exemplified as "substituent" of aforesaid "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4", and these arbitrary substituents of . 1-10, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be substituted.

The "spacer having the number of main chain atoms of 1-8 containing at least one oxygen atom", denotes a divalent group including one or more -O- in the group among aforesaid "spacer having the number of main chain atoms of 1-8". As "spacer having the number of main chain atoms of 1-8 containing at least one oxygen atom", preferably, for example a species in which the oxygen atom is bonded to ring D or the like are nominated.

As "spacer having the number of main chain atoms of 1-6" represented by E, the species in which the 1-6 atoms of main chain are connected among aforesaid "spacer having the number of main chain atoms of 1-8". As "spacer having the number of main chain atoms of 1-6" represented by E, preferably, for example "optionally substituted C1-6 alkylene group", "optionally substituted C1-5 alkylene oxy group" and the like are nominated. Wherein, as "substituent" in "optionally substituted C1-6 alkylene group", "optionally substituted C1-5 alkylene oxy group", for example, species exemplifuied as "substituents" in "optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-4" or the like are nominated, and these arbitrary substituents of 1-8, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be substituted.

As C1-6 alkylene group, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene group and their isomeric groups and the like are nominated.

As C1-5 alkylene oxy group, methylene oxy, ethyleneoxy, trimethylene oxy, tetramethylene oxy, pentamethylene oxy group and their isomeric groups and the like are nominated.

As C1-4 alkylene group, methylene, ethylene, trimethylene, tetramethylene group and their isomeric groups and the like are nominated.

As C1-3 alkylene oxy group, methylene oxy, ethyleneoxy, trimethylene oxy group and their isomeric groups and the like are nominated.

As "3-11-membered monocyclic or bicyclic group" in "3-11-membered optionally substituted monocyclic or bicyclic group" represented by M, for example "3-11-membered monocyclic or bicyclic carbocyclic", "3-11-membered monocyclic or bicyclic heterocyclic containing 1-2 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" and the like are nominated. Wherein, "monocyclic or bicyclic carbocyclic of C3-11" includes monocyclic or bicyclic unsaturated carbon ring of C3-11, carbocyclic ring in which a part thereof or whole is saturated, spiro bonded bicyclic carbocyclic and crosslinked bicyclic carbocyclic. As "monocyclic or bicyclic unsaturated carbon ring of C3-11, carbocyclic ring in which a part thereof or whole is saturated", for example cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydro-naphthalene, tetrahydronaphthalene, perhydronaphthalene ring and the like are proposed, and as "spiro bonded bicyclic carbocyclic ring", for example, spiro[4.4] nonane, spiro[4.5] decane, spiro[5.5] undecane ring and the like are proposed, andas "crosslinked bicyclic carbocyclic ring", for example, bicyclo[2.2.1] heptane, bicyclo[2.2.1] hept-2-ene, bicyclo[3.1.1] heptane, bicyclo[3.1.1] hept-2-ene, bicyclo[2.2.2] octane, bicyclo[2.2.2] oct-2-ene, adamantane, noradamantane ring and the like are nominated. Among these, as "monocyclic or bicyclic aromatic carbon ring of C3-11", for example, benzene, azulene, naphthalene ring and the like are nominated.

Moreover, 3-11-membered monocyclic or bicyclic unsaturated heterocycle containing 1-2 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom, monocyclic or bicyclic unsaturated heterocycle in which a part thereof is saturated, spiro bonded bicyclic heterocyclic

and crosslinked bicyclic heterocyclic rings are included in "3-11-membered monocyclic or bicyclic heterocycle containing 1-2 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom". As "3-11-membered monocyclic or bicyclic unsaturated heterocycle containing 1-2 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom, monocyclic or bicyclic unsaturated heterocycle in which a part thereof is saturated", for example, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepin, diazepine, furan, pyran, oxepine, thiophene, thiopyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazan, oxazine, oxazepine, oxadiazepine, thiazine, thiazepine, thiadiazepin, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, iso benzothiophene, dithia naphthalene, indazole, quinoline, isoquinoline, keno lysine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzo oxazole, benzothiazole, benzimidazole, chromene, benzoxepin, benzoxazepine, benzoxa diazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzoazepin, benzodiazepine, benzofurazan, benzothiadiazole, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazin, tetrahydropyridazine, perhydropyridazine, dihydroazepin, tetrahydroazepin, perhydroazepin, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydro-furan, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thiirane, thietane, dihydro-thiophene, tetrahydrothiophene, dihydrothio pyran, tetrahydrothio pyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydro-oxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isooxazolidine), dihydrothiazol, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxazine, tetrahydrooxazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiazine, tetrahydrothiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydro-benzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroiso benzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathian, dihydrobenzo oxazine,

dihydrobenzo thiazine, dihydrobenzo oxazole, perhydrobenzo oxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzo imidazole, perhydrobenzimidazole, dihydrobenzo azepin, tetrahydrobenzo azepin, dihydrobenzo diazepine, tetrahydrobenzo diazepine, benzo dioxepan, dihydrobenzo oxazepine, tetrahydrobenzo oxazepine, dioxolane, dioxane, dithiolane, dithiane, dioxan indan, benzodioxan, chroman, benzodithiolane, benzodithiane ring and the like are proposed, and as "spiro bonded bicyclic heterocycle", for example, azaspiro[4.4] nonane, oxazaspiro[4.4] nonane, dioxaspiro[4.4] nonane, azaspiro[4.5] decane, thiaspiro[4.5] decane, dithiaspiro[4.5] decane, dioxaspiro[4.5] decane, oxazaspiro[4.5] decane, azaspiro[5.5] undecane, oxaspiro[5.5] undecane, dioxaspiro[5.5] undecane ring and the like are nominated, and as "crosslinked bicyclic heterocycle", for example, azabicyclo[2.2.1] heptane, oxabicyclo[2.2.1] heptane, azabicyclo[3.1.1] heptane, azabicyclo[3.2.1] octane, oxabicyclo[3.2.1] octane, azabicyclo[2.2.2] octane, diazabicyclo[2.2.2] octane ring and the like are nominated. Among these, as "3-11-membered monocyclic or bicyclic aromatic heterocyclic containing 1-2 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" for example pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, furazan, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzooxazole, benzothiazole, benzimidazole, benzofurazan, benzothiadiazole and the like are nominated.

Wherein, as "substituent" in " optionally substituted 3-11-membered monocyclic or bicyclic cyclic group" represented by M, for example, substituents and the like represented in aforesaid RD are proposed, and these arbitrary substituents of 1-10, preferably 1-5, more preferably 1-3 species may be substituted at positions that can be substituted.

In general formula (A), 3-8-membered monocyclic heterocyclic aryl containing at least one nitrogen atom as heteroatom and 0-3 nitrogen atoms, 0-1 oxygen atom and/or 0-1 sulfur atom as other heteroatom, heterocyclic aryl in which a part thereof or whole may be saturated, are included in the 3-8-membered monocyclic heterocycle containing at least one nitrogen atom as heteroatom and 0-3 nitrogen atoms, 0-1 oxygen atom and/or 0-1 sulfur atom as other heteroatom. For example, pyrrole, imidazole, triazole, tetrazole, pyrazole, aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazolin, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazin, tetrahydropyridazine, perhydropyridazine, dihydroazepin, tetrahydroazepin, perhydroazepin, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine,

dihydro-oxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isooxazolidine), dihydrothiazol, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine ring and the like are nominated.

In general formula (A), mono-, di- or tri-cyclic carbocyclic aryl of C3-15, and carbocyclic aryl in which a part thereof or whole may be saturated, are included in the mono-, di- or tri-cyclic carbocyclic of C3-15. For example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridodecane, cyclotetradecane, cyclopentadecane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene, cyclooctadiene, benzene, pentalene, perhydropentalene, azulene, perhydroazulene, indene, perhydroindene, indan, naphthalene, dihydro-naphthalene, tetrahydronaphthalene, perhydronaphthalene, heptalene, perhydroheptalene, biphenylene, a s-indacene, s-indacene, acenaphthalene, acenaphthene, fluorene, phenalene, phenanthrene, anthracene ring and the like are nominated.

In general formula (A), 3-15-membered mono-, di- or tri-cyclic heterocyclic ring containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms, includes 3-15-membered mono-, di- or tri-cyclic heterocyclic aryl containing heteroatomes selected from 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms, and heterocyclic aryl in which a part thereof or whole may be saturated.

As 3-15-membered mono-, di- or tri-cyclic heterocyclic aryl containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms, for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepin, diazepine, furan, pyran, oxepine, thiophene, thio pyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepin, indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline,

benzo oxazole, benzothiazole, benzimidazole, chromene, benzoxepin, benzoxazepine, benzoxa diazepine, benzothiepine, benzothiazepine, benzo thiadiazepine, benzoazepin, benzodiazepine, benzofurazan, benzothiadiazole, benzotriazole, carbazole, beta-carboline, acridine, phenazine, dibenzofuran, xanthene, dibenzothiophene, phenothiazine, phenoxazine, phenoxathiin, thianthrene, phenanthridine, phenanthroline, perimidine ring and the like are nominated. Moreover, as 3-15-membered mono-, di- or tri-cyclic heterocyclic aryl containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms in which a part thereof or whole may be saturated, for example aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, tri azoline, tri azolidine, tetrazolin, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazin, tetrahydropyridazine, perhydropyridazine, dihydroazepin, tetrahydroazepin, perhydroazepin, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydro-furan, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thiirane, thietane, dihydro-thiophene, tetrahydrothiophene, dihydrothio pyran, tetrahydrothio pyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydro-oxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (iso oxazolidine), dihydrothiazol, tetrahydrothiazole (thiazolidine), dihydroiso thiazole, tetrahydroiso thiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine, oxathiane, indoline, isoindoline, dihydro-benzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroiso benzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroiso benzothiophene, perhydroiso benzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathian, dihydrobenzooxazine, dihydrobenzothiazine, pyrazino morpholine, dihydrobenzooxazole, perhydrobenzooxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzoimidazole, perhydrobenzoimidazole, dihydrobenzoazepin,

tetrahydrobenzoazepin, dihydrobenzodiazepine, tetrahydrobenzodiazepine, benzodioxepan, dihydrobenzooxazepine, tetrahydrobenzooxazepine, dihydrocarbazole, tetrahydrocarbozole, perhydrocarbazole, dihydroacridine, tetrahydroacridine, perhydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, perhydrodibenzofuran, perhydrodibenzothiophene, dioxolane, dioxane, dithiolane, dithiane, dioxaindan, benzodioxan, chroman, benzodithiolane, benzodithiane ring and the like are nominated.

In general formula (A), the monocyclic carbocyclic of C3-8 includes monocyclic carbocyclic aryl of C3-8, monocyclic carbocyclic aryl in which a part thereof or whole may be saturated. For example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cyclohepta diene, cyclooctadiene, benzene ring and the like are nominated.

In general formula (A), the 3-8-membered monocyclic heterocyclic ring containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom includes 3-8-membered monocyclic heterocyclic aryl containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom, and monocyclic heterocyclic aryl in which a part thereof or whole may be saturated. As 3-15-membered mono-, di- or tri-cyclic heterocyclic aryl containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom, for example pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepin, diazepine, furan, pyran, oxepine, thiophene, thiopyran, thiepin, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepin ring and the like are nominated. Moreover, as 3-8-membered monocyclic heterocyclic aryl containing 1-4nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom, in which a part thereof or whole is saturated, for example aziridine, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazolin, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydroazepin, tetrahydroazepin, perhydroazepin, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, oxirane, oxetane, dihydro-furan, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrooxepine, tetrahydrooxepine, perhydrooxepine, thiirane, thietane, dihydro-thiophene, tetrahydrothiophene, dihydrothio pyran, tetrahydrothiopyran, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydro-oxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isooxazolidine), dihydrothiazol,

tetrahydrothiazole (thiazolidine), dihydroiso thiazole, tetrahydroiso thiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepin, tetrahydrothiadiazepin, perhydrothiadiazepin, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane ring and the like are nominated.

As C3-4 alkylene group, trimethylene, tetramethylene group and their isomeric groups and the like are nominated.

In this specification, effector cell is a T cell, and all the T cell which is not a naive T cell is included. Wherein, naive T cell denotes a T cell which has not been subjected to antigen stimulation. As effector cell, for example RA negative and/or RO-positive T cells and the like are proposed, as "RA negative and/or RO-positive T cells", for example Th1 cell, Th2 cell, cytotoxic T cell (CTL), Central memory T cell (TCM), effector memory T cell (TEM) and the like are nominated. Wherein, RA and RO denote cell surface antigens, and term "negative" used therein means that the surface antigen cannot be detected, and moreover "positive" means that the surface antigen can be detected. Wherein, as process used for the detection of surface antigen, all detection processes of the surface antigen known to date are included. For example, well known techniques unsed by a person skilled in the art for detection of protein (for example flow cytometry [FACS], immunostaining, Western blot, fluorescein antibody technique or the like) or techniques equivalent to these and the like are nominated. Moreover, TCM and TEM are defined using by the process described in literature (Nature. 1999 Oct. 14, 401 [6754]: 708-12.). In this invention, a preferred effector cell is CCR4-positive effector cell in other words, effector cell expressing CCR4.

In this specification, the function of effector cell includes all the functions of the effector cell in which CCR4 participates. As function of the effector cell in which CCR4 participates, for example, cell migration, facilitation of vascular wall permeability, in filtration into tissue, accumulation in tissue, release of liquid factors, expression of cell surface antigen and the like are nominated.

In this specification, TNF alpha control action denotes an action to regulate the quantity of TNF

alpha in vivo, preferably, an action to reduce the TNF alpha quantity in blood or tissue. In a further embodiment, it denots an action to reduce TNF alpha quantity in blood or tissue in the diseases known to increase the TNF alpha quantity in blood or tissue.

In accordance with this invention, unless specifically indicated to the contrary, the isomers are all included. For example, straight chain species and branched chain species are included in alkyl group, alkenyl group, alkynyl group, alkoxy group, alkylthio group, alkylene group, alkenylene group, alkynylene group. Moreover, isomers due to double bond, ring, condensed ring(E, Z, cis, trans body), isomers due to the presences of asymmetric carbon or the like (R, S body, alpha, beta configuration, enantiomer, diastereomer), optically active bodies (D, L, d, 1-foems) having optical rotation, polar bodies due to chromatographic separation (high polar body, low polarity body), equilibrium compounds, rotational isomers, mixtures of arbitrary proportions of these, racemic mixtures are all included in this invention.

[salts].

Non-toxic salts or pharmacologically permitted salts are all included In the salts of the compound represented by general formula (I). Nontoxic water-soluble salts are preferred as pharmacologically permitted salts. As suitable salt of the compound represented by general formula (I), for example, salts of alkali metal (potassium, sodium, lithium or the like), salts of alkaline earth metal (calcium, magnesium or the like), ammonium salts (tetramethylammonium salt, tetrabutylammonium salt or the like), salts of organic amine (triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, dithanol amine, Tris [hydroxymethyl] methylamine, lysine, arginine, N-methyl-D-glucamine or the like), acid addition salts [inorganic acid salts (hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, nitrate or the like), organic salts (acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzensuplhonate, toluenesulfonate, isethionate, glucuronate, gluconate or the like) or the like] are nominated. In the salts of the compounds of this invention, solventate or solventate of alkali (earth) metal salts, ammonium salts, organic amine salts, acid addition salts of aforesaid compounds of this invention, are also included. It is preferred that solventate is non-toxic and water soluble. As suitable solventate, for example solventate of water, alcohol system solvent (ethanol or the like) or the like are nominated. The compounds of this invention are converted into to non-toxic salt and pharmacologically permitted salt by well known methods.

Furthermore, quaternary ammonium salts are included in the salt. The quaternary ammonium

salts denotes a species in whcih the nitrogen atom of the compound represented by general formula (I) is quaternalised with R0 group (R0 group denotes C1-8 alkyl group, C1-8 alkyl group substituted by phenyl group).

Moreover, N-oxide is also contained in the salt. The compounds of this invention can be formed into N-oxide by arbitrary process. N-oxide denotes the species in which the nitrogen atom of the compound represented by general formula (I) is oxidised.

Prodrug of the compound represented by general formula (I) refers to a compound which is converted to the compound represented by general formula (I) in vivo by reaction using enzyme and gastric acid or the like. As prodrug of the compound represented by general formula (I), when the compound represented by general formula (I) contains amino group, compounds in which the amino group thereof is acylated, alkylated, phosphorylated (for example, compounds in which the amino group of the compound represented by general formula (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxylen-4-yl) methoxy carbonylated, tetrahydrofuranylated, pyrrolidyl methylated, pivaloyloxymethylated, acetoxymethylated, tert-butylated or the like); when the compound represented by general formula (I) contains hydroxy group, compounds in which the hydroxy group thereof is acylated, alkylated, phosphorylated (for example, compounds in which the hydroxy group of the the compound represented by general formula (I) isacetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated, or the like); when the the compound represented by general formula (I) contains carboxy group, compounds in which the carboxy group thereof is esterified or amidated (compounds in which carboxy group of the compound represented by general formula (I) is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, [5-methyl-2-oxo-1,3-dioxylen-4-yl] methyl esterified, cyclohexyloxycarbonylethyl esterified, methyl amidated, or the like) and the like are nominated. These compounds can be produced by itself familiar process. Moreover, the prodrug of the compound represented by general formula (I) may be any of hydrate and non-hydrate. Moreover, the prodrug of the compound represented by general formula (I) may be a species that is changed to the compound represented by general formula (I) under physiological condition as described in Publication "Development of pharmaceutical" Vol. 7 "molecular design" 163-198 pages, Hirokawa Shoten, 1990. Moreover, the compound represented by general formula (I) may be labelled with isotopes (for example 3H, 14C, 35S, 125I and the like).

In general formula (I) of this invention, each of the definition represented by ring A, ring B, ring D, J, G, RD, Rn, E is all preferred. Below preferred groups and preferred rings are listed. However, all the symbols used therein denote same as above meanings.

As "cyclic group" in "optionally substituted cyclic group" represented by ring A, for example carbocyclic, heterocyclic ring and the like are preferred, and more preferably for example "mono-, di- or tri-cyclic carbocyclic of C3-15", "3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" and in particular for example benzene, naphthalene, pyridine, pyrazole, dioxaindan, benzodioxane, cyclopropane, cyclopentane, cyclohexane, furan, thiophene, tetrahydrofuran, piperidine, morpholine, pyridine-1-oxide, 1-methylpyridinium ring or the like are nominated. More particularly preferably for example benzene, naphthalene, pyridine, pyrazole, dioxaindan, benzodioxane ring and the like are nominated.

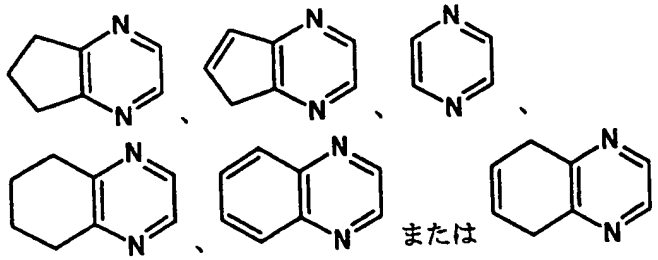
As "substituent" in "optionally substituted cyclic group" represented by ring A, for example, halogen atom, trifluoromethyl group, optionally substituted aliphatic hydrocarbon group, -ORa1 group, -NRa1Ra2 group, optionally substituted 3-15-membered cyclic group or the like are preferred, and more preferably, for example halogen atom, optionally substituted C1-8 alkyl group, hydroxy group, amino group, -O-(C1-8 alkyl) group which may be substituted by -NRb1Rb2 group, and in particular preferably, for example halogen atom, optionally substituted C1-4 alkyl group, hydroxy group, amino group, -O-(C1-4 alkyl) group which may be substituted by -NRb1Rb2 group, or the like are nominated. More particularly preferably, for example fluorine atom, chlorine atom, methyl group, hydroxy group, methoxy group, 2-dimethylaminoethyl oxy group or amino group and the like are nominated.

As "cyclic group" in "optionally substituted cyclic group" represented by ring B, for example carbocyclic, heterocyclic ring and the like are preferred, and more preferably for example "mono-, di- or tri-cyclic carbocyclic of C3-15", "3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" and in particular for example, benzene, pyridine, thiophene, naphthalene, pyrrole, pyrazole, isoxazole, thiazole, benzothiadiazole, benzothiophene, imidazole, benzofurazan, furan, benzopyran ring and the like are nominated. Among "mono-, di- or tri-cyclic carbocyclic of C3-15", "3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom", in particular preferably for example, "monocyclic carbocyclic of C3-8", "3-8-membered monocyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom", or the like are

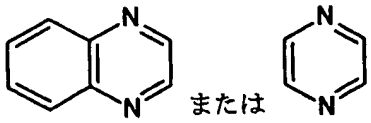
nominated, and among these, "monocyclic carbocyclic of C3-8", "3-8-membered monocyclic aromatic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom", or the like are more preferred. In an embodiment for example, benzene, pyridine, thiophene, furan, pyrrole, pyrazole, isoxazole, thiazole ring and the like are more preferred. In particular preferably, for example benzene, pyridine, thiophene ring or the like are nominated.

As "substituent" in "optionally substituted cyclic group" represented by ring B, preferably for example, substituents selected from the first group, optionally substituted aliphatic hydrocarbon group, substituents selected from the second group, optionally substituted carbamoyl group and the like are proposed, more preferably, for example, optionally substituted aliphatic hydrocarbon group, halogen atom, nitro group, cyano group, trifluoromethyl group, trifluoromethoxy group, -ORa1 group, -NRa1Ra2 group, -SO2Ra1 group, -SRa1 group, -COORa1 group, -CORa1 group and the like, and in particular for example C1-8 alkyl group, halogen atom, nitro group, trifluoromethyl group or the like are preferred. More particularly for example methyl group, fluorine atom, chlorine atom, bromine atom, nitro group, trifluoromethyl group and the like are preferred.

As "cyclic group" in "optionally substituted cyclic group" represented by ring D, for example carbocyclic, heterocyclic ring and the like are preferred, and more preferably for example "3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" or the like and in particular for example, "3-10-membered mono- or di-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" or the like. As "3-10-membered mono- or di-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom", preferably for example "3-10-membered mono- or di-cyclic heterocycle containing 1-4 nitrogen atoms as heteroatom" or the like and more preferably "3-10-membered mono- or di-cyclic heterocycle containing 1-2 nitrogen atoms as heteroatom" or the like, and in particular preferably, for example,



or the like are nominated. In particular preferably, for example,

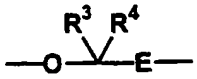


or the like are nominated.

As "substituent" in "optionally substituted cyclic group" represented by ring D, preferably for example, optionally substituted aliphatic hydrocarbon group, halogen atom, cyano group, trifluoromethyl group, -COORa1 group, optionally substituted 3-15-membered cyclic group are preferred, and more preferably, for example, C1-8 alkyl group, halogen atom, trifluoromethyl group or optionally substituted C3-10 monocyclic of or bicyclic carbocyclic ring or the like are nominated. In particular preferably, for example methyl group, chlorine atom, bromine atom, trifluoromethyl group or optionally substituted benzene ring and the like are nominated.

As as preferred G, for example a spacer having the number of main chain atoms of 1-4 and the like are nominated, more preferably, for example, a spacer having the number of main chain atoms of 1-4 containing at least one nitrogen atom, or the like are nominated, and in particular preferably, for example, -NRT1-, -NRT1-SO2-, -NRT1-CO-, -NRT1-CO-NRT2-, -NRT1-SO2-NRT2-, -NRT1-COO-, -NRT1-O-, -NRT1-NRT2-, -NRT1-W-, -SO2-NRT1-, -CO-NRT1-, -OCO-NRT1-, -O-NRT1-, -W-NRT1- or the like are nominated. Among these, -NRT1-SO2- (in this group, it is assumed that the nitrogen atom is bonded to ring D and the sulfur atom is bonded to ring B) is preferred, and more particularly, for example -NH-SO2- (in this group, it is assumed that the nitrogen atom is bonded to ring D and the sulfur atom is bonded to ring B) and the like are preferred.

As preferred J, for example a spacer having the number of main chain atoms of 1-8 and the like are nominated, and more preferably for example a spacer having the number of main chain atoms of 1-8 containing at least one oxygen atom and the like, and in particular preferably, for example the species in which the oxygen atom is bonded to ring D and the like are nominated. In a further embodiment, for example



(in this group, every symbol has the same aforesaid meanings) and the like re preferred, wherein, as R3 and R4, for example hydrogen atom or methyl group or the like are preferred, E is preferably for example a bond, C1-6 alkylene group or C1-5 alkylene oxy and the like, more preferably for example a bond, C1-4 alkylene group, C1-3 alkylene oxy group, or the like are nominated. In particular preferably as E, for example, a bond, methylene group or methylene

oxy group or the like are nominated. Wherein, as C1-5 alkylene oxy group described as preferred group of E, C1-3 alkylene oxy group described as more preferred group, and methylene oxy group described as in particular preferred group, wherein the species in which the oxygen atom is bonded to ring A is more preferred.

In this invention, compounds of general formula (I) including combinations of preferred groups and preferred rings listed above, are preferred. The compounds represented by general formula (A) are in particular preferred.

In general formula (A) of this invention, each of the definition represented by R1, R2, R3, R4, R5, R6, E1, ring AI, ring B1, p and q is all preferred. Below preferred groups and preferred ring sare listed. However, all the symbols used therein denote the same as above meanings.

As ring A1, for example "monocyclic or bicyclic carbocyclic of C3-10" or "3-10-membered monocyclic or bicyclic heterocyclic containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" or the like are preferred, more preferably, for example "monocyclic or bicyclic carbocyclic aryl of C3-10 " or "3-10-membered monocyclic or bicyclic heterocyclic aryl containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom or heterocyclic aryl in which a part thereof may be saturated" or the like. It is in particular preferably for example benzene, naphthalene, pyridine, pyrazole, dioxaindan or benzodioxane ring.

As preferred R5, it is for example halogen atom, C1-8 alkyl group, -OR31 or -NR32R33 or the like, more preferably, for example halogen atom, C1-4 alkyl group, hydroxy group, C1-4 alkoxy group, C1-4 alkyloxy group substituted by -NR37R38 group, or amino group or the like. It is in particular preferably for example chlorine atom, methyl group, hydroxy group, methoxy group, 2-dimethylaminoethyl oxy group or amino group or the like.

As p, preferably it is 0, 1 or 2.

As ring B1, preferably for example "monocyclic carbocyclic ring of C3-8", "monocyclic 3-8-membered heterocyclic containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" or the like are nominated, more preferably, for example "monocyclic carbocyclic aryl of C3-8", " monocyclic 3-8-membered heterocyclic aryl containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom", or the like are nominated. It is in particular preferably for example benzene, pyridine or thiophene ring or the like.

As preferred R6, for example, substituents other than Cyc2 among the substituents listed above as R6. More preferably, it is for example C1-8 alkyl group, halogen atom or the like, and in particular preferably for example C1-4 alkyl group, halogen atom or the like are nominated. More particularly, for example methyl group, fluorine atom, chlorine atom or bromine atom and the like are preferred.

As q, preferably it is 0, 1 or 2.

As R1 and R2, preferably it is for example hydrogen atom, C1-8 alkyl group, halogen atom, trifluoromethyl group, cyano group, Cyc1 or the like, and more preferably, for example, hydrogen atom, C1-4 alkyl group, halogen atom, trifluoromethyl group, cyano group or "mono-, bi- or tri-cyclic carbocyclic of C3-15" or the like. In particular preferably, for example, hydrogen atom, methyl group, chlorine atom, bromine atom, trifluoromethyl group, cyano group or benzene ring or the like are nominated. Moreover, -CH=CH-CH=CH- formed by linking R1 and R2 is preferred, too.

As preferred Cyc1, it is preferably for example "monocyclic carbocyclic of C3-8" or "3-8-membered monocyclic heterocycle of containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom" or the like, and more preferably, for example cyclopropane, cyclobutane, cyclopentane, cyclohexane, benzene, imidazole, pyridine, piperidine or morpholine ring or the like are nominated.

As R18 that is the substituent of Cyc1, it is preferably for example NR21R22 or -COR23, or the like and in particular preferably for example NH2 or -CHOLINE or the like are nominated.

As R3 and R4, it is preferably for example hydrogen atom or methyl group or the like.

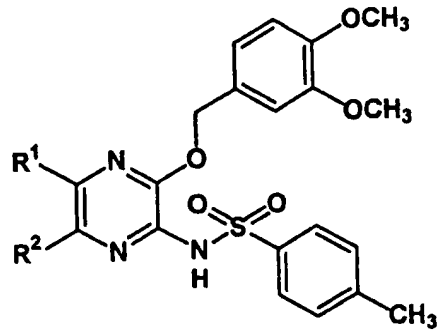
As preferred E1, it is for example single bond, C1-4 alkylene group or C1-3 alkylene oxy group or the like. It is in particular preferably for example single bond, methylene group or methylene oxy group or the like.

Compounds of general formula (A) including the combinations of preferred groups and preferred rings listed above are preferred among the compounds of this invention represented by general formula (I), in particular compounds of this invention which represent with general formula (A).

As preferred compounds of this invention, for example, compounds or salts thereof described in Examples and the like are nominated.

Among the compounds of this invention represented by general formula (I), in particular the compounds of this invention represent by general formula (A), as preferred compounds, pyrazine derivatives or salts thereof represented by:

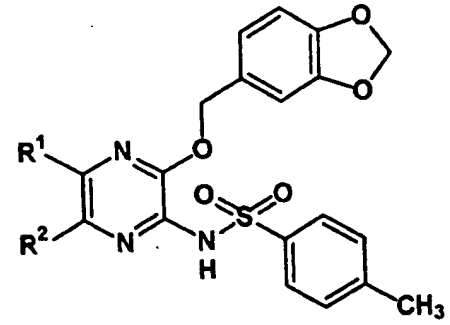
General formula (I-1)



(I－1)

(wherein, R1 and R2 have the same aforesaid meanings),

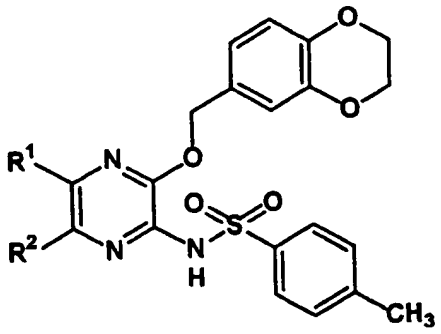
General formula (I-2)



(I－2)

(wherein, R1 and R2 have the same aforesaid meanings),

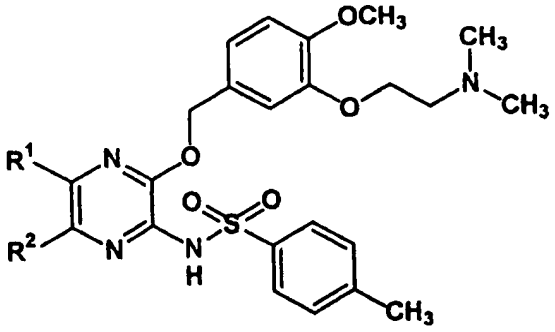
General formula (I-3)



(I－3)

(wherein, R1 and R2 have the same aforesaid meanings),

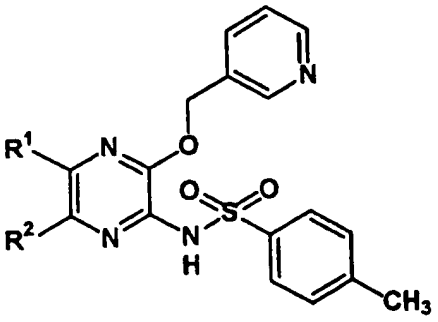
General formula (I-4)



(I－4)

(wherein, R1 and R2 have the same aforesaid meanings),

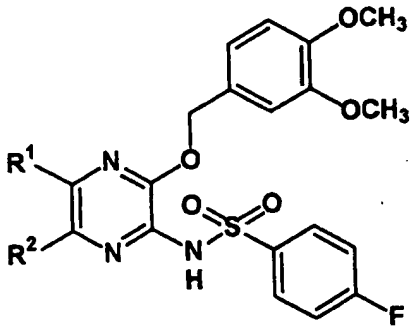
General formula (I-5)



(I－5)

(wherein, R1 and R2 have the same aforesaid meanings),

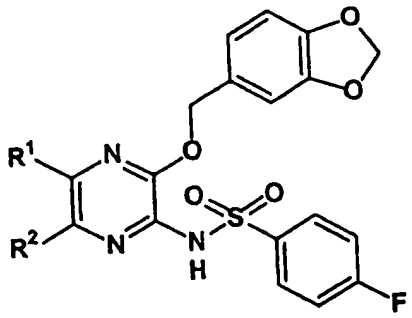
General formula (I-6)



(I－6)

(wherein, R1 and R2 have the same aforesaid meanings),

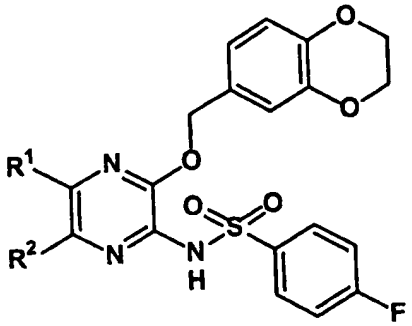
General formula (I-7)



(I－7)

(wherein, R1 and R2 have the same aforesaid meanings),

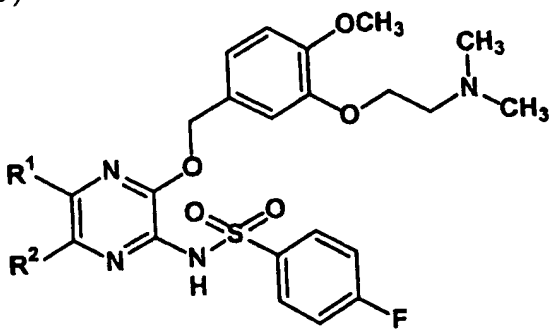
General formula (I-8)



(I－8)

(wherein, R1 and R2 have the same aforesaid meanings),

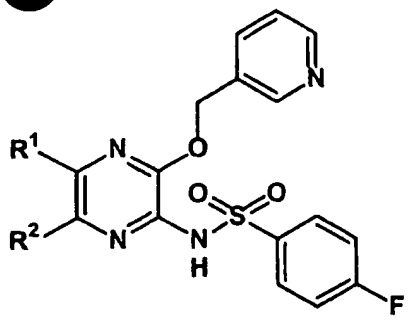
General formula (I-9)



(I－9)

(wherein, R1 and R2 have the same aforesaid meanings),

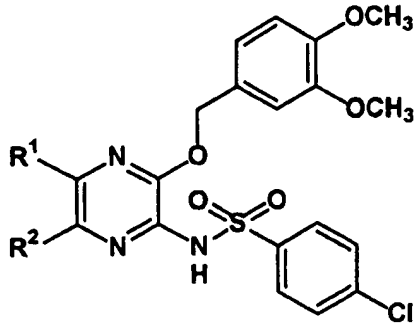
General formula (I-10)



(I－10)

(wherein, R1 and R2 have the same aforesaid meanings),

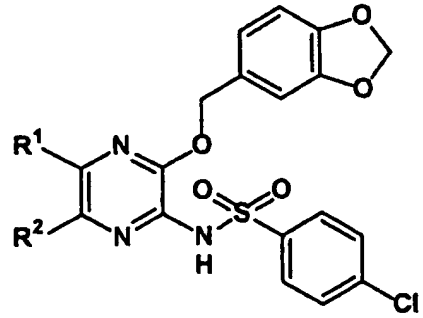
General formula (I-11)



(I－11)

(wherein, R1 and R2 have the same aforesaid meanings),

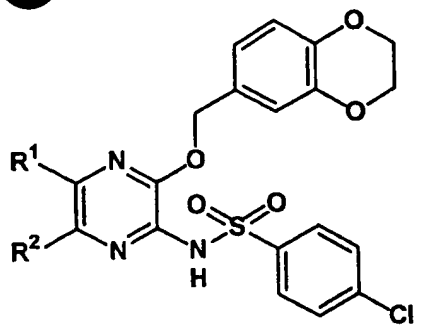
General formula (I-12)



(I－12)

(wherein, R1 and R2 have the same aforesaid meanings),

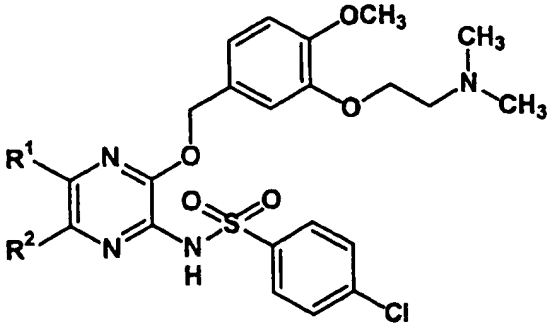
General formula (I-13)



(I-13)

(wherein, R1 and R2 have the same aforesaid meanings),

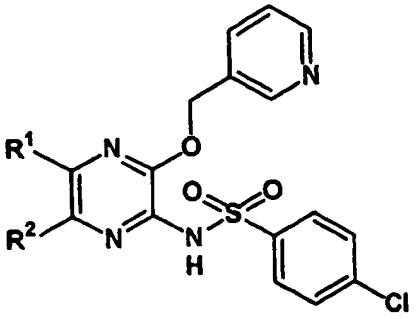
General formula (I-14)



(I-14)

(wherein, R1 and R2 have the same aforesaid meanings),

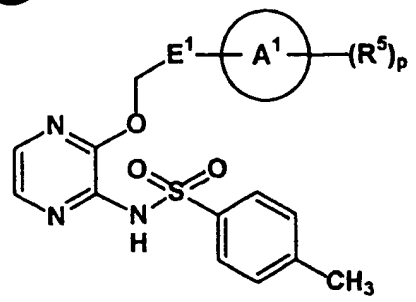
General formula (I-15)



(I-15)

(wherein, R1 and R2 have the same aforesaid meanings),

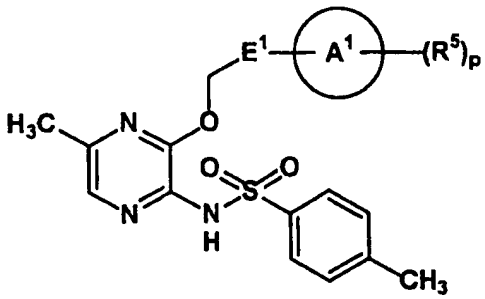
General formula (I-16)



(I－16)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

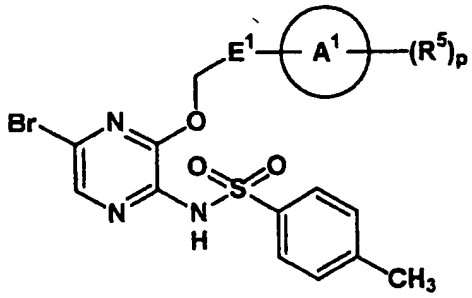
General formula (I-17)



(I－17)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

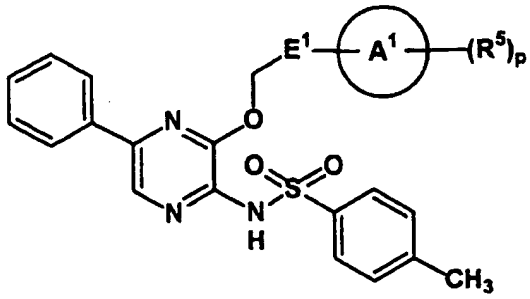
General formula (I-18)



(I－18)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

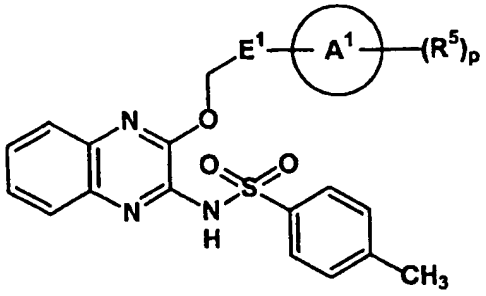
General formula (I-19)



(I－19)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

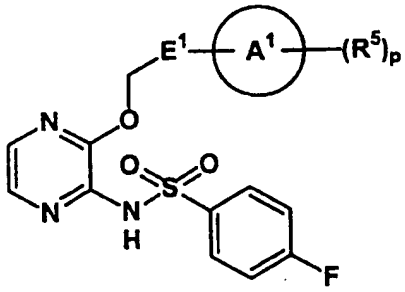
General formula (I-20)



(I-20)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

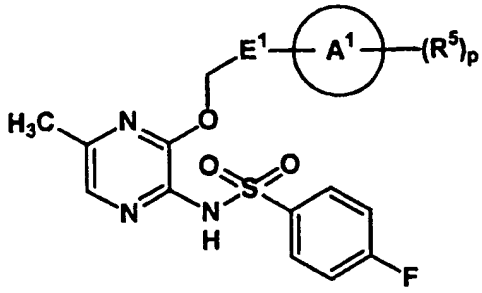
General formula (I-21)



(I-21)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

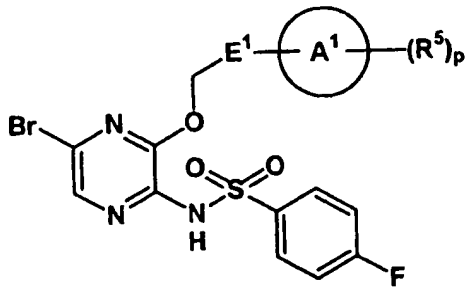
General formula (I-22)



(I-22)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

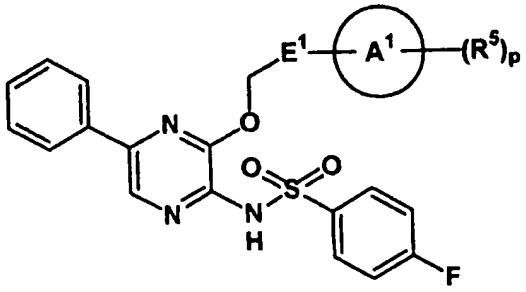
General formula (I-23)



(I－23)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

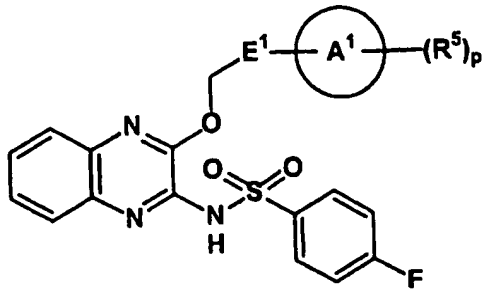
General formula (I-24)



(I－24)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

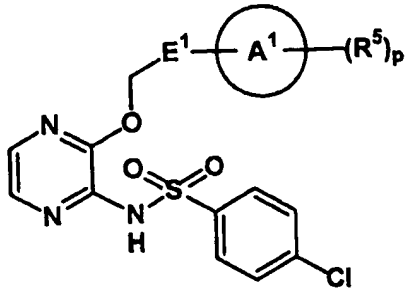
General formula (I-25)



(I－25)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

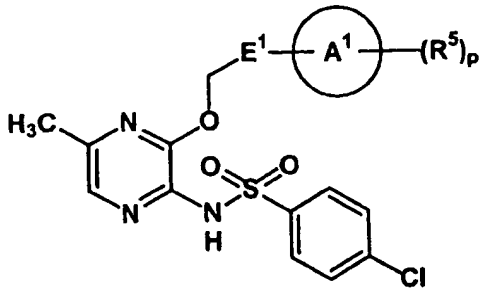
General formula (I-26)



(I－26)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

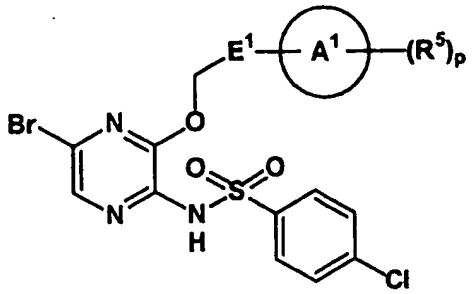
General formula (I-27)



(I－27)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

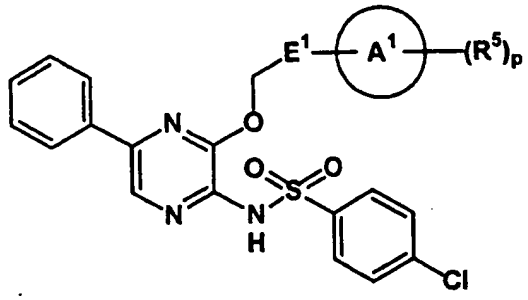
General formula (I-28)



(I－28)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

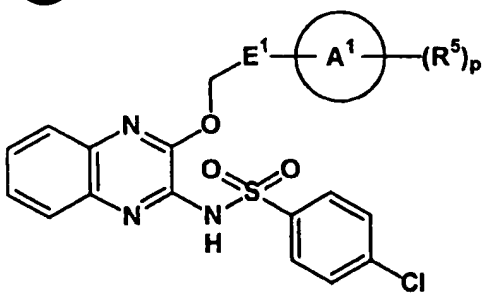
General formula (I-29)



(I－29)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings),

General formula (I-30)

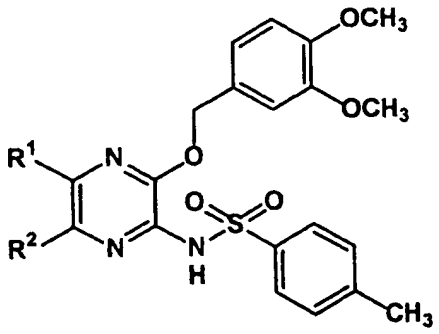


(I－30)

(wherein, E1, ring A1, R5 and p have the same aforesaid meanings).

As example compounds of this invention, compounds shown in the following tables 1-30, compounds described in Examples, salts thereof and the like are nominated.

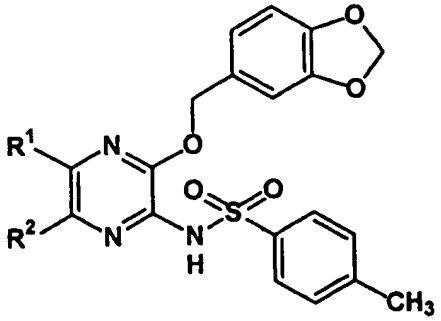
Table 1



(I－1)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

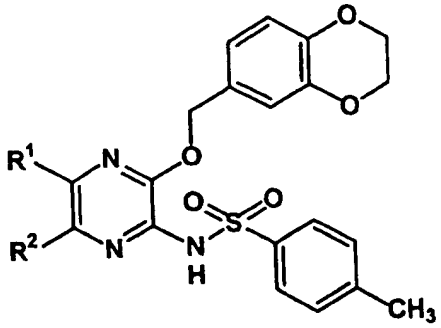
Table 2



(I－2)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

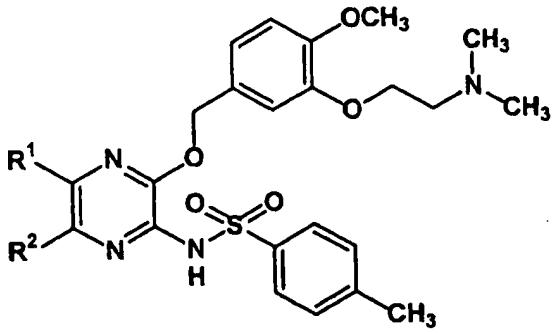
Table 3



(I – 3)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

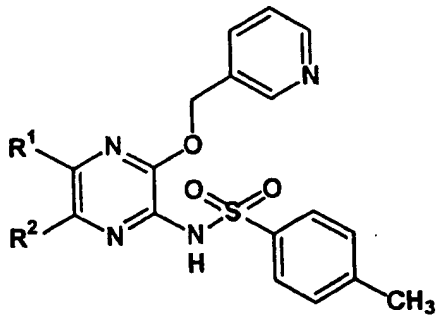
Table 4



(I－4)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

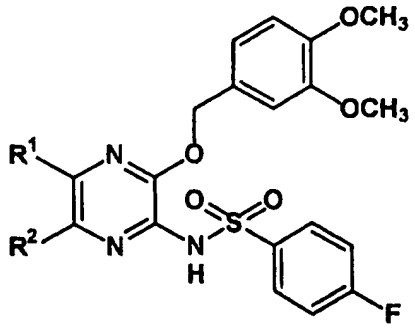
Table 5



(I－5)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

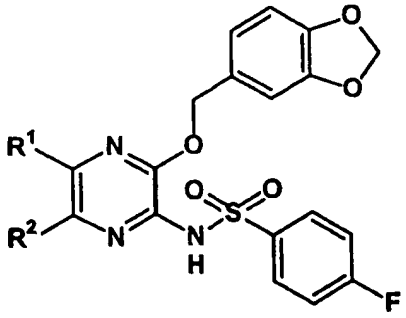
Table 6



(I－6)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

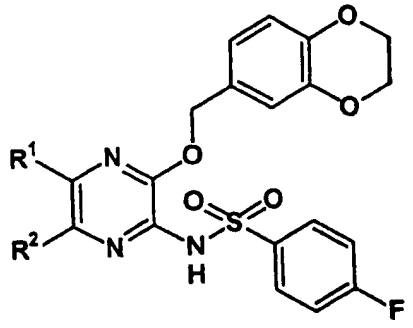
Table 7



(I－7)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

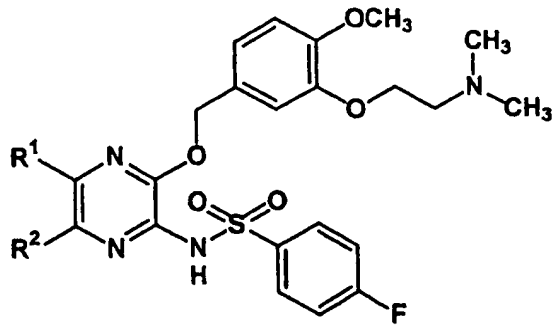
Table 8



(I－8)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

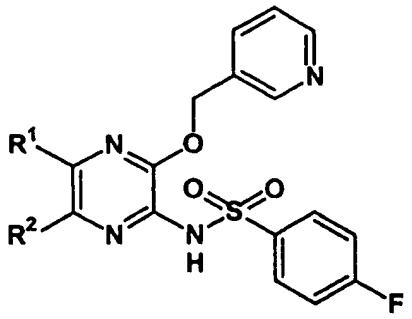
Table 9



(I－9)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

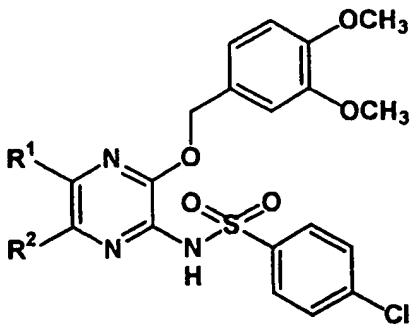
Table 10



(I－10)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

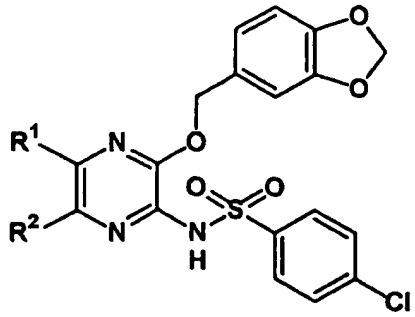
Table 11



(I－11)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

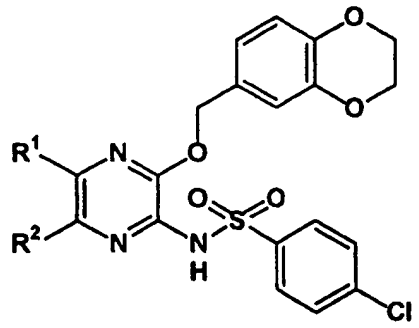
Table 12



(I－12)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

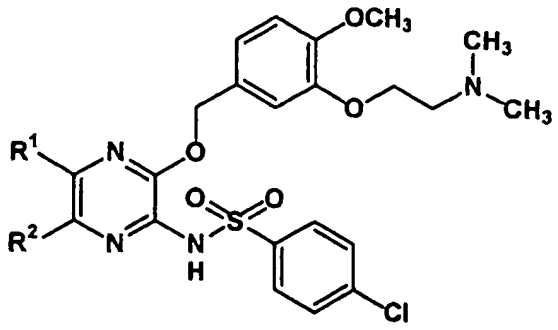
Table 13



(I－13)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl.	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

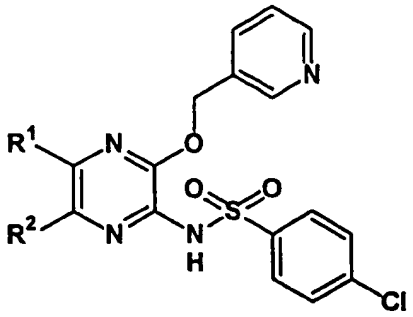
Table 14



(I－14)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

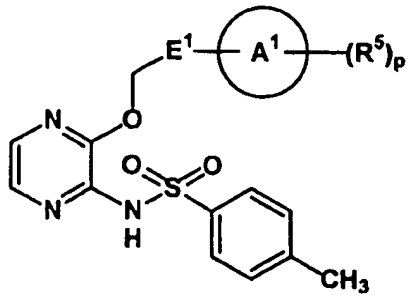
Table 15



(I－15)

No.	R^1	R^2	No.	R^1	R^2
1	H	H	11	H	CH_3
2	CH_3	H	12	H	OCH_3
3	OCH_3	H	13	H	Cl
4	Cl	H	14	H	Br
5	Br	H	15	H	Ph
6	Ph	H	16	H	CN
7	CN	H	17	H	NO_2
8	NO_2	H	18	H	COOH
9	COOH	H	19	$-(CH_2)_4-$	
10	$-(CH_2)_3-$		20	-CH=CH-CH=CH-	

Table 16



(I－16)

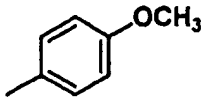
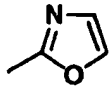
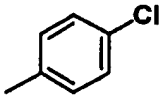
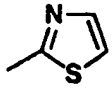
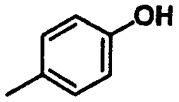
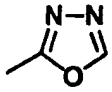
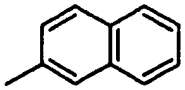
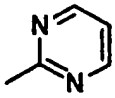
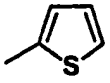
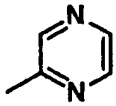
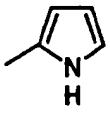
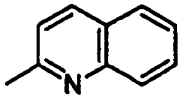
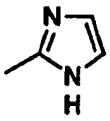
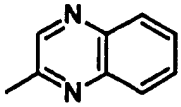
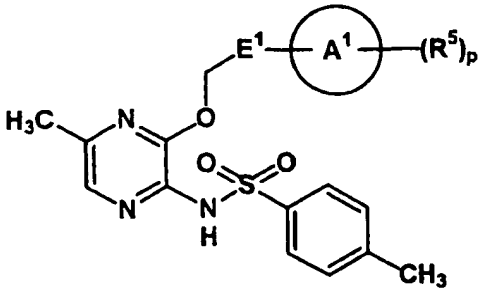
No.	—E¹—A¹—(R⁵)ₚ	No.	—E¹—A¹—(R⁵)ₚ
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 17



(I－17)

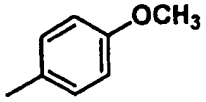
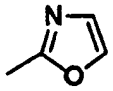
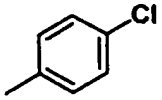
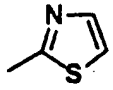
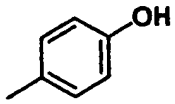
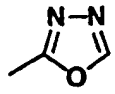
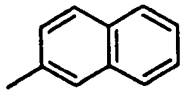
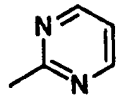
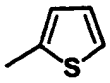
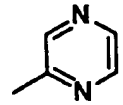
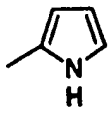
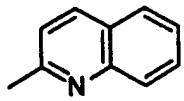
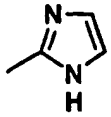
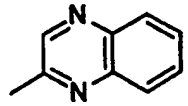
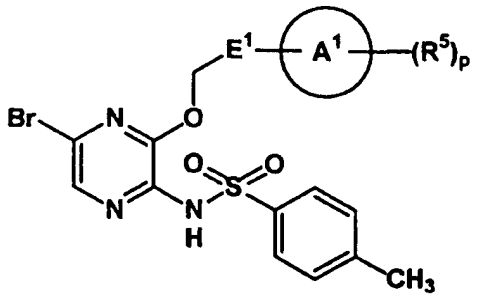
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 18



(I－18)

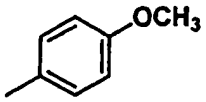
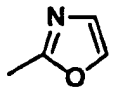
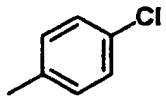
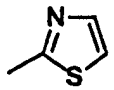
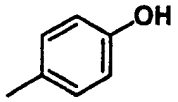
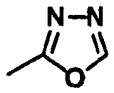
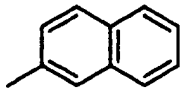
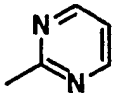
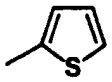
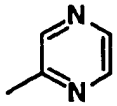
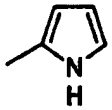
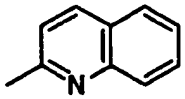
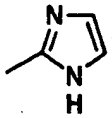
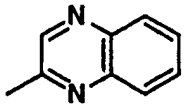
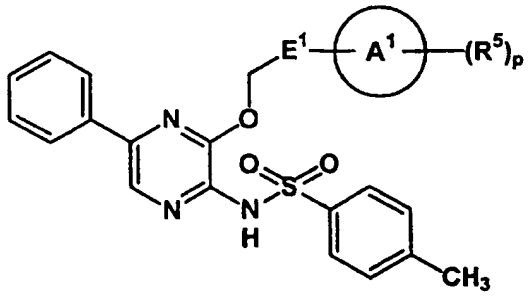
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 19



(I－19)

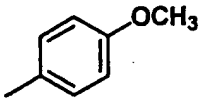
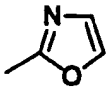
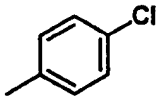
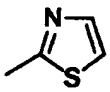
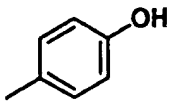
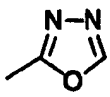
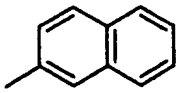
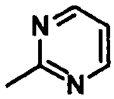
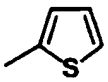
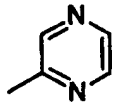
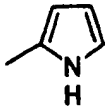
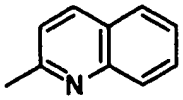
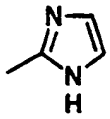
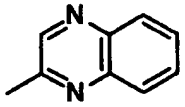
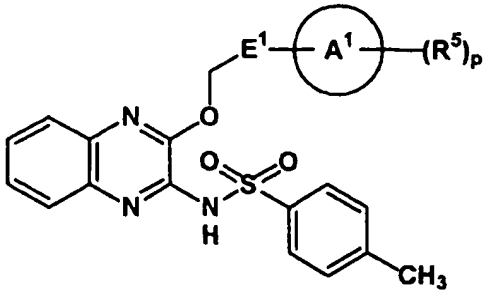
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 20



(I－20)

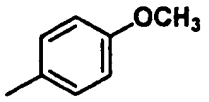
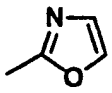
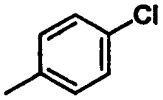
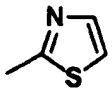
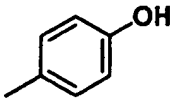
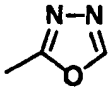
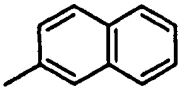
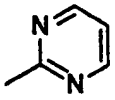
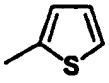
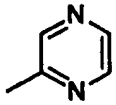
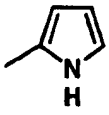
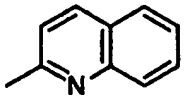
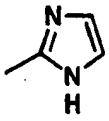
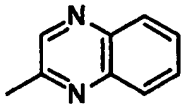
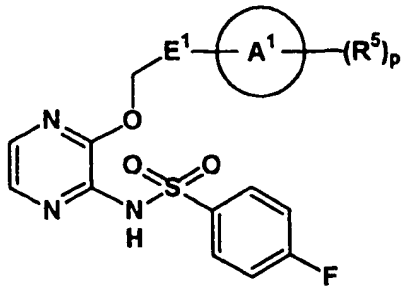
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 21



(I－21)

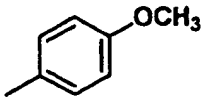
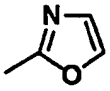
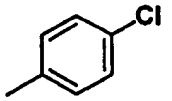
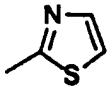
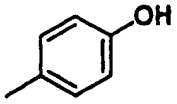
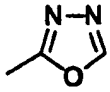
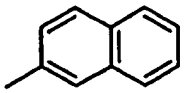
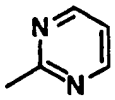
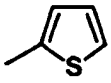
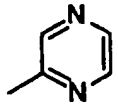
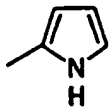
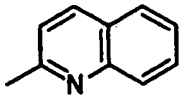
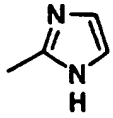
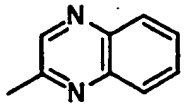
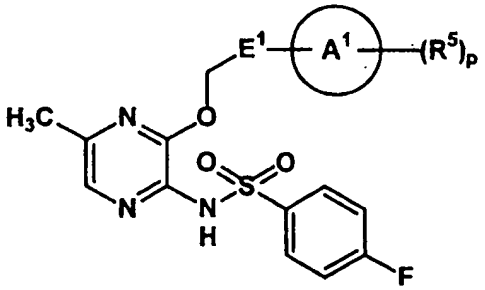
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 22



(I－22)

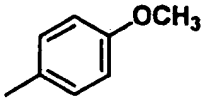
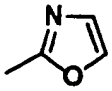
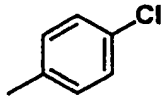
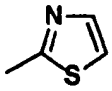
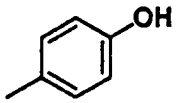
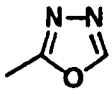
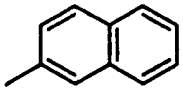
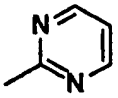
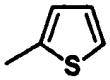
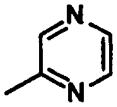
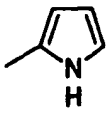
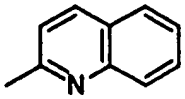
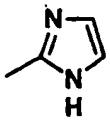
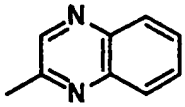
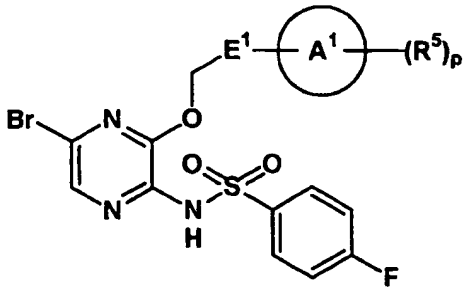
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 23



(I－23)

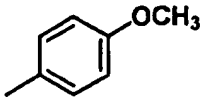
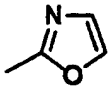
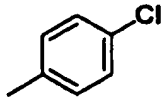
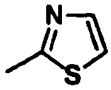
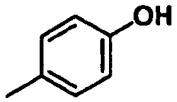
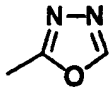
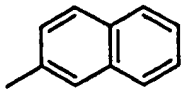
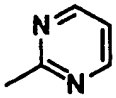
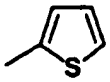
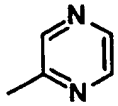
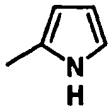
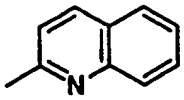
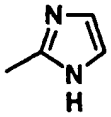
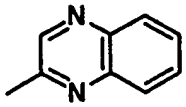
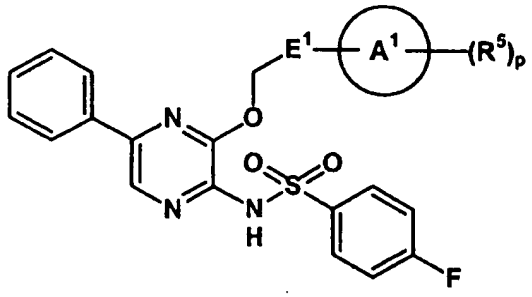
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 24



(I－24)

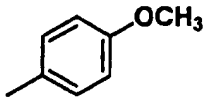
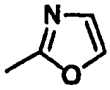
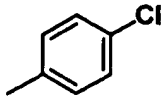
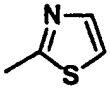
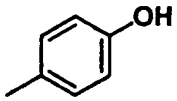
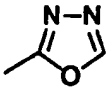
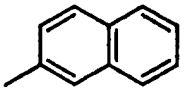
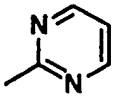
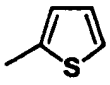
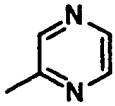
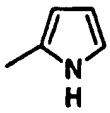
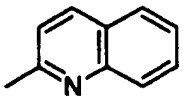
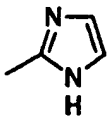
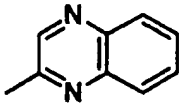
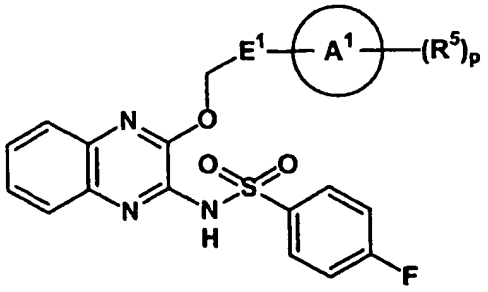
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 25



(I－25)

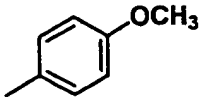
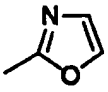
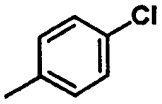
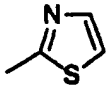
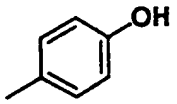
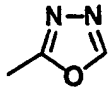
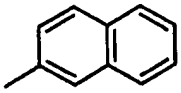
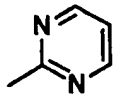
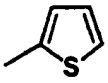
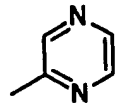
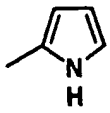
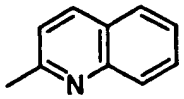
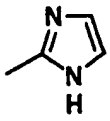
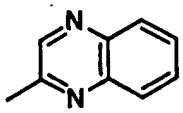
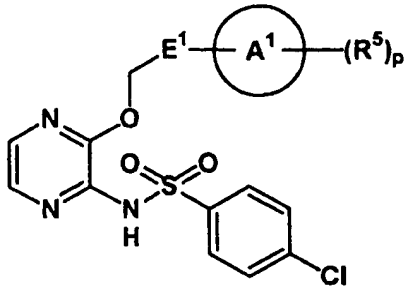
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 26



(I－26)

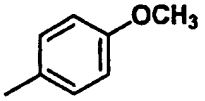
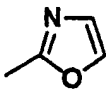
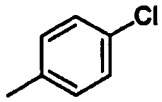
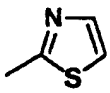
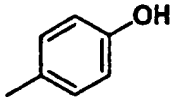
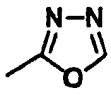
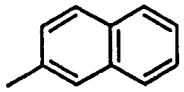
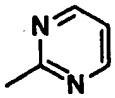
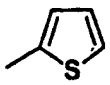
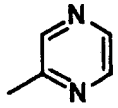
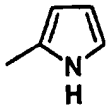
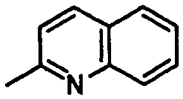
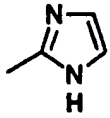
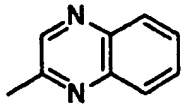
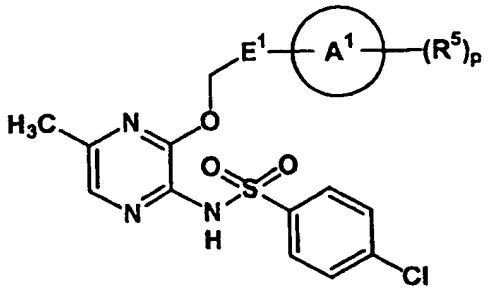
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 27



(I－27)

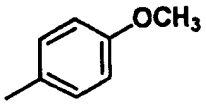
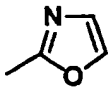
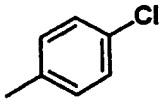
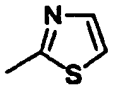
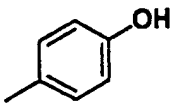
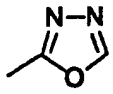
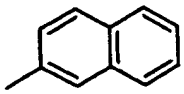
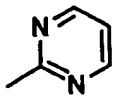
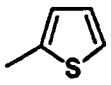
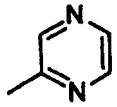
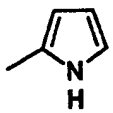
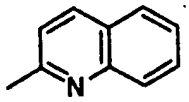
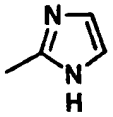
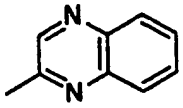
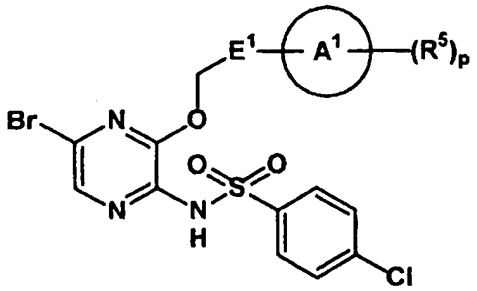
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 28



(I－28)

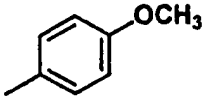
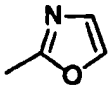
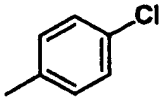
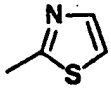
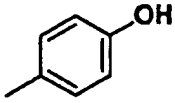
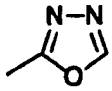
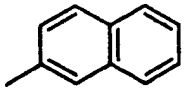
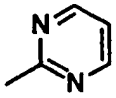
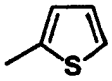
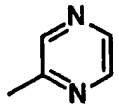
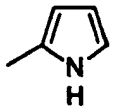
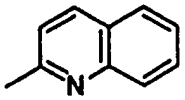
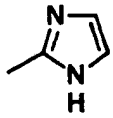
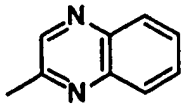
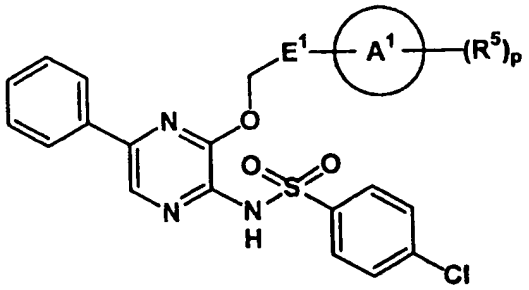
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Table 29



(I－29)

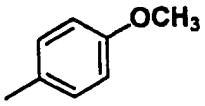
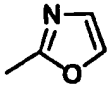
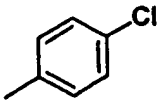
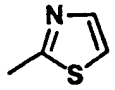
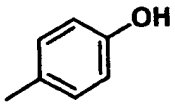
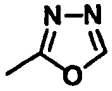
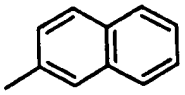
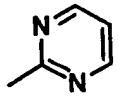
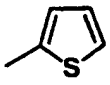
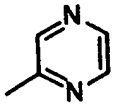
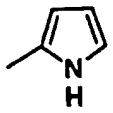
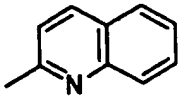
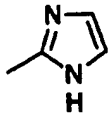
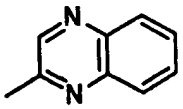
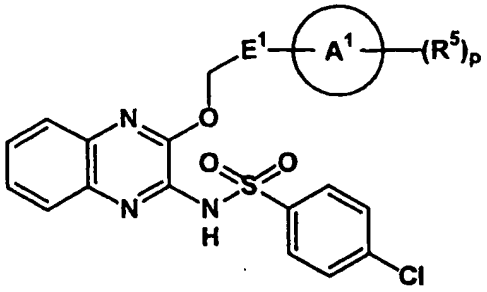
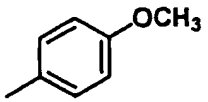
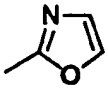
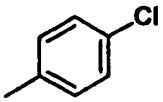
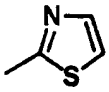
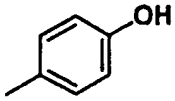
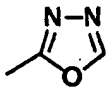
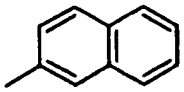
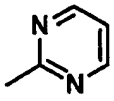
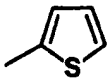
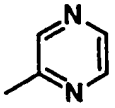
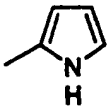
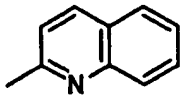
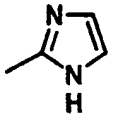
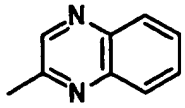
No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

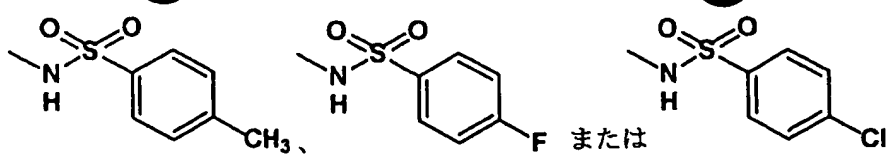
Table 30



(I－30)

No.	—E¹—A¹—(R⁵)p	No.	—E¹—A¹—(R⁵)p
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	
7		14	

Moreover, as preferred compounds, compounds in which in the aforesaid compounds (I-1)-compounds (I-30), the substituents represented by

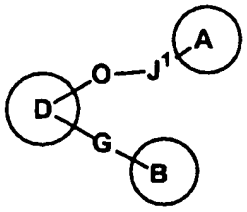


are replaced with (thiophen-2-yl) sulfonyl amino group, (2,3-dichloro thiophen-5-yl) sulfonyl amino group, (2,5-dichloro thiophen-3-yl) sulfonyl amino group, 2,3-dichlorophenyl sulfonyl amino group, 2-methyl-3-chlorophenyl sulfonyl amino group, 2-trifluoromethylphenyl sulfonyl amino group, 2-chlorophenyl sulfonyl amino group, 2-bromo phenylsulfonyl amino group, 2-chloro-4-fluorophenyl sulfonyl amino group, 2,6-dichlorophenyl sulfonyl amino group, 3-bromo phenylsulfonyl amino group, 2,4-difluorophenyl sulfonyl amino group, 2-methylphenyl sulfonyl amino group, 3-chloro-4-methylphenyl sulfonyl amino group, 3-chlorophenyl sulfonyl amino group, 2-fluorophenyl sulfonyl amino group, 2,3,4-trichlorophenyl sulfonyl amino group, 2,4-dichlorophenyl sulfonyl amino group, 2,6-difluorophenyl sulfonyl amino group, 2-cyanophenyl sulfonyl amino group, 2,4,6-trichlorophenyl sulfonyl amino group, phenylsulfonyl amino group, 3-nitro-4-methylphenyl sulfonyl amino group, 3-nitrophenyl sulfonyl amino group, 4-bromo phenylsulfonyl amino group, 3-methylphenyl sulfonyl amino group, 2,5-difluoro-4-bromo phenylsulfonyl amino group, 3-trifluoromethylphenyl sulfonyl amino group, 2-trifluoromethoxyphenyl sulfonyl amino group, 3-methoxyphenyl sulfonyl amino group, 4-chloro-2,5-dinethylphenyl sulfonyl amino group, 2,4-dichloro-6-methylphenyl sulfonyl amino group, 4-trifluoromethyl-2-chloro phenyl sulfonyl amino group, 2-methyl-4-fluorophenyl sulfonyl amino group, 3-nitro-4-chlorophenyl sulfonyl amino group, 2-methoxycarbonylphenyl sulfonyl amino group, 2-methoxy-5-methylphenyl sulfonyl amino group, 4-ethylphenyl sulfonyl amino group, 2,5-dichloro phenyl sulfonyl amino group, 4-trifluoromethoxy sulfonyl amino group 2,4,5-trichlorophenyl sulfonyl amino group, 4-(2-propyl) phenylsulfonyl amino group, 4-(2-methoxyphenyl oxy) phenylsulfonyl amino group, 2-nitro-4-methoxyphenyl sulfonyl amino group, 4-nitrophenyl sulfonyl amino group, 2,5-dimethoxyphenyl sulfonyl amino group, 2-methyl-5-nitrophenyl sulfonyl amino group, 4-butoxy phenylsulfonyl amino group, 2-methoxy-4-methylphenyl sulfonyl amino group, 2-methoxy-5-butylphenyl sulfonyl amino group, 3,5-dimethyl phenylsulfonyl amino group, 2,3,6-trimethyl-4-methoxyphenyl sulfonyl amino group, 2-methoxy-5-chlorophenyl sulfonyl amino group, 2,4,6-trimethylphenyl sulfonyl amino group or 4-methoxyphenyl sulfonyl amino group are also preferred.

Processes for the production of the compounds of this invention

The compounds of this invention represented by general formula (I) can be produced by combinations of well known methods, for example, processes shown below, processes described in Examples or processes described in Comprihensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock John Wiley & Sons Inc, 1999) or the like.

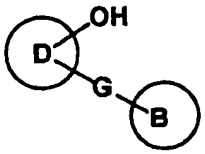
Among the compounds of this invention represented by general formula (I), the compound in which J is bonded with ring D via oxygen atom, in other words, the compound represented by general formula (I-A)



(I-A)

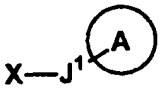
(wherein, J1 denotes a bond or spacer having the number main chain atoms of 1-7, and the other symbols have the same aforesaid meanings) can be produced by processes of (a-1) and (b-1) shown below.

(a-1): The compound of this invention represented by general formula (I-A) can be produced by a process wherein a compound represented by general formula (II)



(II)

(in the formula, all symbols have the same aforesaid meanings) and a compound compound represented by general formula (III)



(III)

(wherein, X denotes leaving group (the leaving group for example means halogen atom, methanesulphonyl oxy group (OMs group), p-toluenesulfonyl oxy group (OTs group), trifluoromethane sulfonyl oxy group (OTf group), or the like), are subjected to etherification reaction, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin are carried out.

This etherification reaction is well known, and is carried out for example in an organic solvent (N,N-dimethylformamide, dimethylsulfoxide, chloroform, methylene chloride, diethyl ether, tetrahydrofuran, methyl t-butyl ether, 1,4-dioxane, 1,2-dimethoxyethane or the like) by reacting at 0-120°C in the presence of a base [hydride of alkali metal (sodium hydride, potassium hydride or the like), organic metal reagent (n-butyllithium or the like), quaternary ammonium salt (fluorinated tetrabutyl ammonium or the like) or the like].

The compounds in which at least one group in general formula (I-A) contains carboxyl group, hydroxy group, amino group or thiol group, can be produced by subjecting the compounds in which each group is protected with protecting group, to deprotecting reaction.

As protecting group of carboxyl group, for example, methyl group, ethyl group, allyl group, t-butyl group, trichloroethyl group, benzyl (Bn) group, phenacyl group and the like are nominated.

As protecting group of hydroxy group, for example, methyl group, trityl group, methoxymethyl (MOM) group, 1-ethoxyethyl (EE) group, methoxyethoxy methyl (MEM) group, 2-tetrahydropyranyl (THP) group, trimethylsilyl (TMS) group, triethylsilyl (TBS) group, t-butyldimethylsilyl (TBDMS) group, t-butyl diphenyl silyl (TBDPS) group, acetyl (Ac) group, pivaloyl group, benzoyl group, benzyl (Bn) group, p-methoxybenzyl group, allyloxycarbonyl (Alloc) group, 2,2,2-trichloroethoxycarbonyl (Troc) group and the like are nominated.

As protecting group of amino group, for example, benzyloxycarbonyl group, t-butoxycarbonyl group, allyloxycarbonyl (Alloc) group, 1-methyl-1-(4-biphenyl) ethoxycarbonyl (Bpoc) group, trifluoroacetyl group, 9-fluorenylmethoxycarbonyl group, benzyl (Bn) group, p-methoxybenzyl group, benzyloxymethyl (BOM) group, 2-(trimethylsilyl) ethoxymethyl (SEM) group and the like are nominated.

As protecting group of thiol group, for example, benzyl group, methoxybenzyl group, methoxymethyl (MOM) group, 2-tetrahydropyranyl (THP) group, diphenylmethyl group, acetyl (AC) group are nominated.

The protecting groups of carboxyl group, hydroxy group, amino group or thiol group are not restricted in particular in addition to aforesaid groups, as long as it can be easily and selectively eliminated. For example, groups described in Protective groups in Organic Synthesis (T.W. Greene, John Wiley & Sons Inc, 1999) are used.

Deprotecting reaction of protecting groups of carboxyl group, hydroxy group, amino group or thiol group is known well, and for exampl,

(1) Alkaline hydrolysis,

(2) deprotecting reaction under acidic condition,

(3) deprotecting reaction by hydrogenoltsis,

(4) deprotecting reaction of silyl group,

(5) deprotecting reaction using metal,

(6) deprotecting reaction using organic metal, and the like are nominated.

When these processes are described in concrete terms:

(1) Deprotecting reaction by alkaline hydrolysis, is carried out for example, in an organic solvent (methanol, tetrahydrofuran, 1,4-dioxane or the like) at a temperature of 0-40°C using hydroxide of alkali metal (sodium hydroxide, potassium hydroxide, lithium hydroxide or the like), hydroxide of alkaline earth metal (barium hydroxide, calcium hydroxide or the like) or carbonate (sodium carbonate, potassium carbonate or the like) or an aqueous solution thereof or a mixture thereof.

(2). Deprotecting reaction under acidic condition is performed, for example, in an organic solvent (methylene chloride, chloroform, 1,4-dioxane, ethyl acetate, anisole or the like) at a temperature of 0-100°C in an organic acid (acetic acid, trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid and the like) or an norganic acid (hydrochloric acid, sulfuric acid and the like) or a mixture thereof (hydrogen bromide / acetic acid and the like).

(3). Deprotecting reaction by hydrogenolysis is performed for example at a temperature of 0-200°C in the presence of ammonium formate under hydrogen atmosphere at normal pressure or under pressure in the presence of catalyst (palladium-carbon, palladium black, palladium hydroxide, platinum oxide, Raney nickel or the like), in a solvent (ether system (tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, diethyl ether or the like), alcohol system (methanol, ethanol or the like), benzene system (benzene, toluene or the like), ketone system (acetone, methyl ethyl ketone or the like), nitrile system (acetonitrile or the like), amide system (N,N-dimethylformamide or the like), water, ethyl acetate, acetic acid or mixed solvent of 2 or more thereof or the like).

(4). Deprotecting reaction of silyl group is carried out for example by reacting at temperature of -20 to 40°C using a fluoride (fluorinated tetrabutyl ammonium, hydrogen fluoride aqueous solution, hydrogen fluoride-pyridine complex or the like) in an organic solvent miscible with water (tetrahydrofuran, acetonitrile or the like).

(5). Deprotecting reaction using metal is carried out for example in an acid medium (acetic acid, buffer of pH4.2-7.2 or a liquid mixture of those solutions and organic solvent such as tetrahydrofuran and the like) in the presence of powder zinc with or without application of ultrasound, at a temperature of 0-40°C.

(6). Deprotecting reaction using metal complex body is carried out for example in an organic solvent (methylene chloride, N,N-dimethylformamide, tetrahydrofuran, ethyl acetate, acetonitrile, 1,4-dioxane, ethanol or the like), water or a mixed solvent thereof, in the presence of trapping reagent (hydrogenated tributyl tin, triethylsilane, dimedone, morpholine, diethylamine, pyrrolidine or the like), organic acid (acetic acid, formic acid, 2-ethyl hexanoic acid and the like) and/or organic salt (2-ethyl hexanoic acid sodium salt, 2-ethyl hexanoic acid potassium or the like) in the absence or presence or phosphine system reagent (triphenyl phosphine or the like) using a metallic complex (tetrakis triphenylphosphine palladium (0), dichloro bis (triphenylphospphine) palladium (II), palladium (II) acetate, tris chloride (triphenylphosphine) rhodium (I) or the like) at a temperature of 0-40°C.

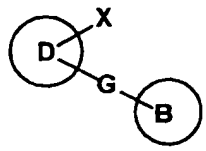
Moreover, in addition to aforesaid processes, deprotecting reaction can be carried out, for example, by processes described in Protective groups in Organic Synthesis (T.W. Greene, John Wiley & Sons Inc, 1999).

Moreover, when there is a moiety within the molecule which is bonded to resin and the resin thereof is polystyrene resin, the compounds of this invention can be cleaved from the resin by the following process. This cleavage reaction from the resin is well known, and for example is is carried out in an organic solvent (methylene chloride, 1,2-dichloromethane, toluene or the like) by racting at 0-100°C using acid (acetic acid, trifluoroacetic acid, hydrochloric acid and the like).

Although it can be readily understood to a person skilled in the art, the the target compounds of this invention can be readily produced by selecting these deprotecting reactions.

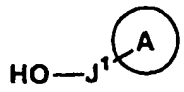
Futhermore, when necessary, an operation to convert to a target non-toxic salt may be performed to by well known method after this reaction.

(b-1): The compounds of this invention represented by general formula (I-A) can be produced by a process wherein a compound represented by general formula (IV)



(IV)

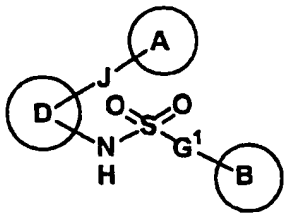
(in the formula, all symbols have the same aforesaid meanings) and compound represented by general formula (V)



(V)

(in the formula, all symbols have the same aforesaid meanings) are subjected to reaction same as in aforesaid (a-1), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out. Deprotecting reaction of protecting group can be carried out by the same process as in the item mentioned above. Moreover, when there is a moiety within the molecule which is bonded to resin and the resin thereof is polystyrene resin, the compounds of this invention can be cleaved from the resin by the same process as in the item mentioned above.

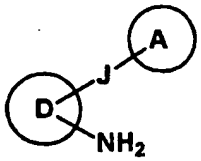
Among the compounds of this invention represented by general formula (I), the compounds wherein G is bonded to ring D via -NHSO-, in other words, the compound represented by general formula (I-B)



(I-B)

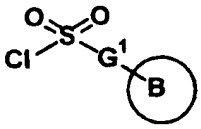
(wherein, G1 denotes a spacer having the number of main chain atoms of 1-2, and the other symbols have the same aforesaid meanings) can be produced by the process (a-2) and (b-2) shown below.

(a-2): The compounds of this invention represented by general formula (I-B) can be produced by subjecting a compound represented by general formula (VI)



(VI)

(in the formula, all symbols have the same aforesaid meanings) and a compound represented by general formula (VII)

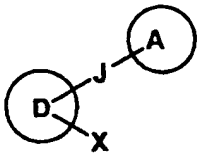

(VII)

(in the formula, all symbols have the same aforesaid meanings) to sulphonamidation reaction.

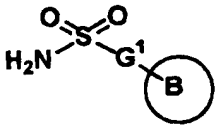
This sulphonamidation reaction is well known, and for example, it is carried out by reacting at 0-40°C in the presence of base (diisopropyl ethylamine, pyridine, triethylamine, N,N-dimethylaniline, N,N-dimethylaminopyridine, sodium hydride, potassium hydride or the like) in an organic solvent (chloroform, methylene chloride, 1,2-dichloromethane, diethyl ether, tetrahydrofuran or the like).

The compounds in which at least one group in general formula (I-B) contains carboxyl group, hydroxy group, amino group or thiol group, can be produced by subjecting the compounds in which each group is protected with protecting group, to deprotecting reaction. Deprotecting reaction of protecting group can be carried out by the same process as in the item mentioned above. Moreover, when there is a moiety within the molecule which is bonded to resin and the resin thereof is polystyrene resin, the compounds of this invention can be cleaved from the resin by the same process as in the item mentioned above.

(b-2). The compounds of this invention represented by general formula (I-B) can be produced by a process wherein a compound represented by general formula (VIII)


(VIII)

(in the formula, all symbols have the same aforesaid meanings) and compound represented by general formula (IX)


(IX)

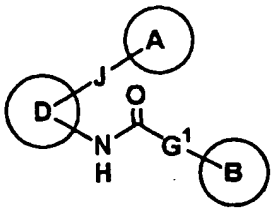
(in the formula, all symbols have the same aforesaid meanings) are reacted, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

This reaction is well known, and, it is carried out for example by reacting at 0-200°C in the presence or absence of base (potassium carbonate, cesium carbonate, triethylamine, n-butyllithium, sodium hydride, sodium hydroxide or the like) in an organic solvent (N,N-

dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide or the like) .

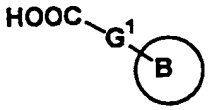
Deprotecting reaction of protecting group can be carried out by the same process as in the item mentioned above. Moreover, when there is a moiety within the molecule which is bonded to resin and the resin thereof is polystyrene resin, the compounds of this invention can be cleaved from the resin by the same process as in the item mentioned above.

Among the compounds of this invention represented by general formula (I), the compound wherein G is bonded to ring D via -NHCO-, in other words, the compound represented by general formula (I-C)



(I-C)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein the compound the general formula (VI) and a compound represented by general formula (X)



(X)

(in the formula, all symbols have the same aforesaid meanings) are subjected to amidation reaction and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

This amidation reaction is weel known, and for example,

(1) a process using acid halide,

(2) a process using mixed acid anhydride,

(3) a process using condensing agent, and the like are nominated.

(1) The process using acid halide can be carried out for example by a process wherein a carboxylic acid is reacted wtih acid halide forming agent (oxalyl chloride, thinyl chloride or the like) in an organic solvent (chloroform, methylene chloride, diethylether, tetrahydrofuran or the like) or in the absence of solvent at -20°C to reflux temperature, the obtained acid halide is reacted with amine in the presence of base (pyridine, triethylamine, N,N-diemthylaniline, N,N-dimethylaminopyridine, diisopropylethylamine or the like) in an inert organic solvent

(chloroform, methylene chloride, diethylether, tetrahydrofuran or the like). Moreover, it can also be carried out by reacting with acid halide at 0-40°C using an aqueous alkali solution (aqueous sodium hydrogen carbonate solution, aqueous sodium hydroxide solution, or the like) in an organic solvent (1,4-dioxxane, tetrahydrofuran or the like).

(2) The process using mixed acid anhydride can be carried out for example by a process wherein a carboxylic acid is reacted wtih acid halide (pivaroyl chloride, p-toluene sulfonyl chloride, methane sulfonyl chloride or the like), or acid derivative (ethyl chloroformate, isobutyl chloroformate, or the like) at 0-40°C, in an organic solvent (chloroform, methylene chloride, diethylether, tetrahydrofuran or the like) or in the absence of solvent, in the presence of base (pyridine, triethylamine, N,N-diemthylaniline, N,N-dimethylaminopyridine, diisopropylethylamine or the like), the obtained mixed acid anhydride is reacted with amine in an organic solvent (chloroform, methylene chloride, diethylether, tetrahydrofuran or the like) at 0-40°C.

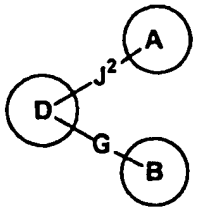
(3) The process using condensing agent can be carried out for example by a process wherein a carboxylic acid and amine are reacted in an organic solvent (chloroform, methylene chloride, diethylether, tetrahydrofuran or the like) or in the absence of solvent, in the presence or absence of base (pyridine, triethylamine, N,N-diemthylaniline, N,N-dimethylaminopyridine, diisopropylethylamine or the like), using a condensing agent (1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino) propyl] carbodiimide (EDC), 1,3-diisopropyl carbodiimide (DIC), 1,1'-carbonyldiimidazole (CDI), 2-chloro-1-methylpyridinium iodine, 1-propyl phosphonic acid cyclic anhydride (PPA) or the like), and using or not using 1-hydroxy benz triazole (HOBt) at 0-40°C.

It is desirable that the reactions of these (1), (2) and (3) in each case are carried out under anhydrous condition in an inert gas (argon, nitrogen or the like) atmosphere.

The compounds in which at least one group in general formula (I-C) contains carboxyl group, hydroxy group, amino group or thiol group, can be produced by subjecting the compounds in which each group is protected with protecting group, to deprotecting reaction. Deprotecting reaction of protecting group can be carried out by the same process as in the item mentioned above. Moreover, when there is a moiety within the molecule which is bonded to resin and the resin thereof is polystyrene resin, the compounds of this invention can be cleaved from the resin by the same process as in the item mentioned above.

Among the compounds of this invention represented by general formula (I), the compounds in

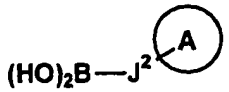
which J is bonded to ring D or a bond via carbon atom, in other words, the compound represented by general formula (I-D)



(I-D)

(in the formula, J2 denotes the same meaning as J, however, the atom that is bonded to ring D or a bond is carbon atom, and other symbols have the same aforesaid meanings) can be produced by processes (a-3) and (b-3) shown below.

(a-3): The compounds of this invention represented by general formula (I-D) can be produced by a process wherein the compound represented by the general formula (IV) and a compound represented by general formula (XI)



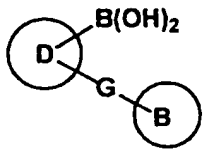
(XI)

(in the formula, all symbols have the same aforesaid meanings) are reacted, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The reaction of compound represented by the general formula (IV) and compound the general formula (XI) is well known, and it can be carried out, for example in an organic solvent (benzene, toluene, N,N-dimethylformamide, 1,4-dioxane, tetrahydrofuran, methanol, acetonitrile, 1,2-dimethoxyethane, acetone or the like) in the presence of base (sodium ethylate, sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, sodium bicarbonate, potassium carbonate, cesium carbonate, carbonic acid thallium salt, phosphoric acid three potassium, cesium fluoride, barium hydroxide, fluorinated tetrabutyl ammonium or the like) or aqueous solution thereof, or, a mixture thereof and catalyst (tetrakis (triphenyl phosphine) palladium (Pd[PPh3]4), bis dichloride (triphenylphosphine) palladium (PdC12[PPh3]2), palladium acetate (Pd(OAc)2), palladium black, 1,1'-bis (diphenylphosphino ferrocene) dichloropalladium (PdC12[dppf]2), diallyl palladium dichloride (PdC12[allyl]2), phenyl bis (triphenylphosphine) palladium iodide, at 10-120°C.

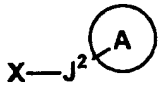
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

(b-3). The compounds of this invention represented by general formula (I-D) can be produced by a process wherein compound represented by general formula (XII)



(XII)

(in the formula, all symbols have the same aforesaid meanings) and a compound represented by general formula (XIII)

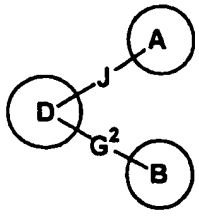


(XIII)

(in the formula, all symbols have the same aforesaid meanings), are subjected to the reaction same as in aforesaid reaction of compound represented by general formula (IV) and compound represented by general formula (XI), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processed.

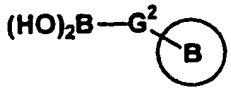
Among the compounds of this invention represented by general formula (I), the compounds in which G is bonded to ring D or bond via carbon atom, in other words, the compound represented by general formula (I-E)



(I-E)

(in the formula, G2 denotes tha same meanings as G, however the atom that is bonded to ring D or bond s carbon atom, and the other symbols have the same aforesaid meanings) can be produced by processes (a-4) and (b-5) shown below.

(a-4): The compounds of this invention represented bygeneral formula (I-E) can be produced by a process wherein the compound represented by the general formula (VIII) and a compound represented by general formula (XIV)

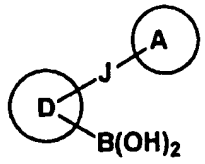


(XIV)

(in the formula, all symbols have the same aforesaid meanings) are reacted in the same way as in the reaction of aforesaid compound represented by the general formula (IV) and compound represented by the general formula (XI), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

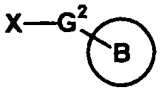
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

(b-4): The compounds of this invention represented bygeneral formula (I-E) can be produced by a process wherein a compound represented by the general formula (XV)



(XV)

(in the formula, all symbols have the same aforesaid meanings) and a compound represented by general formula (XVI)

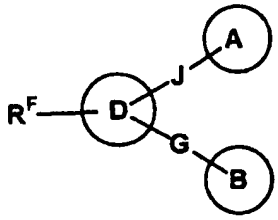


(XVI)

(in the formula, all symbols have the same aforesaid meanings) are subjected to the reaction same as in reaction of aforesaid compound represented by general formula (IV) and compound represented by general formula (XI), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

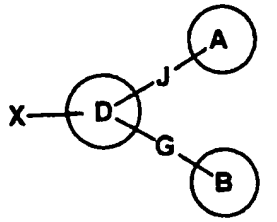
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among the compounds of this invention represented by general formula (I), the compounds in which one of hte substituents of the ring D is C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group, in other words, the compounds represented by general formula (I-F)



(I-F)

(wherein, RF denotes C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group, and the other symbols have the same aforesaid meaning) can be produced by a process wherein a compound represented by general formula (XVII)



(XVII)

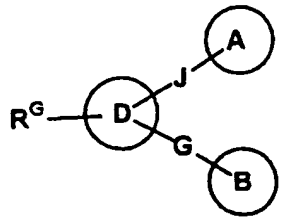
(in the formula, all symbols have the same aforesaid meanings) is subjected to alkylation reaction, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

This alkylation reaction is well known, and for example, it is carried out by reacting in the presence of organic metal reagent (methyl magnesium bromide, n-butyllithium, ethinyl magnesium bromide or the like) and catalyst ([1,3-bis [diphenylphosphino] propane] dichloro nickel (II) (NiCl2(dppp)) or the like) at 0-40°C in an organic solvent (tetrahydrofuran, diethyl ether or the like).

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among the compounds of this invention represented by general formula (I), the compounds in which one of the substituents of the ring D is optionally substituted cyclic group, in other words, the compounds represented by general formula (I-G)



(I-G)

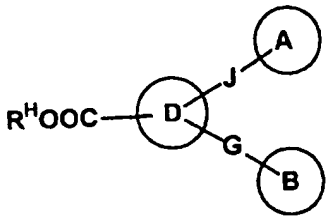
(wherein, RG denotes optionally substituted cyclic group, and the other symbols have the same aforesaid meanings) can be produced by a process wherein the compound represented by general formula (XVII) and a compound represented by general formula (XVIII)

Rg-B(OH)2 (XVIII)

(in the formula, all symbols have the same aforesaid meanings) are subjected to the reaction same as in reaction of aforesaid compound represented by general formula (IV) and compound represented by general formula (XI), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among the compounds of this invention represented by general formula (I), the compounds in which one of the substituents of the ring D denotes COORa1 and Ra1 denotes other than hydrogen atom, in other words, the compounds general formula (I-H)



(I-H)

(wherein, RH denotes the same meaning as Ra1 except hydrogen atom, and other symbols have the same aforesaid meanings) can be produced by a process wherein aforesaid compound represented by general formula (XVII) and a compound represented by general formula (XIX)

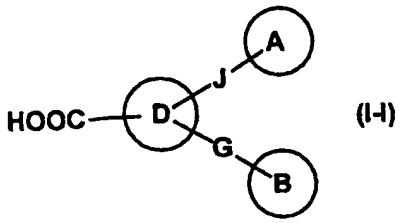
$$R^H\text{-}OH \qquad (XIX)$$

(in the formula, all symbols have the same aforesaid meanings) are reacted in an carbon monoxide atmosphere, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The reaction of compound of general formula (XVII) and compound of general formula (XIX) is well known, and it is carried out, for example in an organic solvent (N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, 1,2-dimethoxyethane or the like) in the presence of base (triethylamine, diisopropyl ethylamine, N-methylmorpholine or the like) and catalyst (tetrakis (triphenyl phosphine) palladium (Pd[PPh3]4), bis dichloride (triphenyl phosphine) palladium (PdC12[PPh3]2)) such as palladium acetate (Pd(OAc)2), palladium black, 1,1'-bis (diphenyl phosphinoferrocene) dichloropalladium (PdC12[dppf]2), diallyl palladium dichloride (PdC12[allyl]2), phenylbis (triphenyl phosphine) palladium iodide (PhPdI[PPh3]2) or the like), in carbon monoxide atmosphere at 10-120°C.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among the compounds of this invention represented by general formula (I), the compounds in which one of the substituents of the ring D represents COOH, in other words, the compounds represented by general formula (I-I)

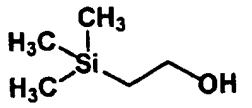


(I-I)

(in the formula, all symbols have the same aforesaid meanings) can be produced by the processes (a-5) and (b-5) shown below.

(a-5): The compounds of this invention represented by general formula (I-I) can be produced by subjecting aforesaid ester compound represented by general formula (I-H) to deprotecting reaction. Deprotecting reaction of protecting group can be carried out by the same process as in the item mentioned above.

(b-5). The compounds of this invention represented by general formula (I-I) can be produced by a process wherein aforesaid compound represented by general formula (XVII) and 2-trimethylsilyl ethanol represented by formula (XX)



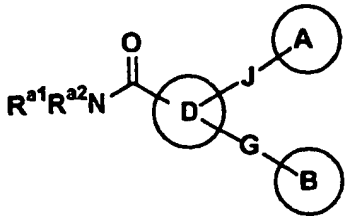
(XX)

are reacted in the presence of carbon monoxide gas, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The reaction of compound represented by general formula (XVII) and compound represented by formula (XX) is carried out by the process same as in aforesaid reaction of compound of general formula (XVII) and compound represented by general formula (XIX).

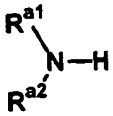
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among the compounds of this invention represented by general formula (I), the compounds in which one of the substituents of the ring D represents CONRBIRR2, in other words, the compounds represented by general formula (I-J)



(I-J)

(in the formula, all symbols have the same aforesaid meanings), can be produced by a process wherein the compound represented by general formula (I-I) produced by aforesaid process and a compound represented by general formula (XXI)



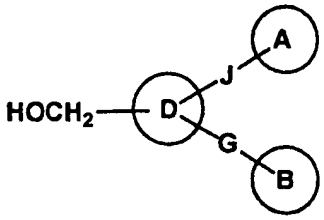
(XXI)

(in the formula, all symbols have the same aforesaid meanings) are subjected to the same amidation reaction used for the synthesis of compound represented by aforesaid general formula

(I-C), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among the compounds of this invention represented by general formula (I), the compounds in which one of the substituents of the ring D represents CH2OH, in other words, the compounds represented by general formula (I-K)



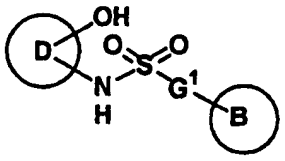
(I-K)

(in the formula, all symbols have the same aforesaid meanings), can be produced by a process wherein a compound represented by general formula (I-H) or a compound represented by general formula (I-I) produced by aforesaid process is subjected to reductive reaction, and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

This reductive reaction is well known, and it can be carried out, for example in an organic solvent (tetrahydrofuran, diethyl ether or the like), in the presence of reducing agent (sodium borohydride, lithium borohydride, lithium aluminium hydride, diisobutylaluminum hydride, borane-dimethylsulfide complex or the like) at -20 to 100°C.

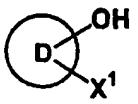
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among compounds the general formula (II), the compounds in which G is bonded to ring D via -NHSO2-, in other words, the compounds represented by general formula (II-B)



(II-B)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein a compound represented by general formula (XXII)



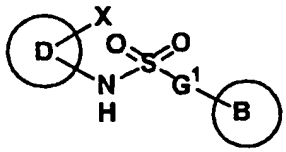
(XXII)

(wherein, X1 has same definitions as X, and other symbols have the same aforesaid meanings)

and the compound represented by general formula (IX) are subjected to the reaction same as in aforesaid (b-2), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

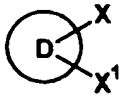
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among compounds represented by general formula (IV), the compounds in which G is bonded to ring D via -NHSO2-, in other words, the compounds represented by general formula (IV-B)



(IV-B)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein a compound represented by general formula (XXIII)

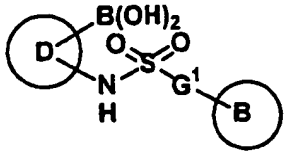


(XXIII)

(in the formula, all symbols have the same aforesaid meanings) and the compound of general formula (IX) are subjected to the reaction same as in aforesaid (b-2), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

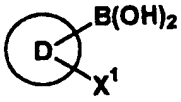
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among compounds represented by general formula (XII), the compounds in which G is bonded to ring D via -NHSO2-, in other words, the compounds represented by general formula (XII-B)



(XII-B)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein a compound represented by general formula (XXIV)

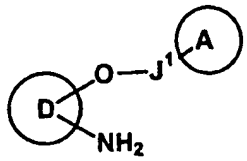


(XXIV)

(in the formula, all symbols have the same aforesaid meanings) and the compound represented by general formula (IX) are subjected to the reaction same as in aforesaid (b-2), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

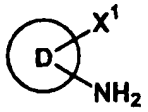
The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among compounds represented by general formula (VI), the compounds in which J is bonded to ring D via oxygen atom, in other words, the compounds represented by general formula (VI-B)



(VI-B)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein a compound represented by the general formula (XXV)

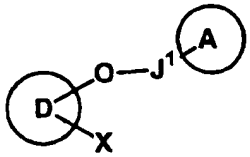


(XXV)

(in the formula, all symbols have the same aforesaid meanings) and a compound represented by general formula (V) are subjected to the reaction same as in aforesaid (a-1), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among compounds represented by general formula (VIII), the compounds in which J is bonded to ring D via oxygen atom, in other words, the compounds represented by general formula (VIII-B)

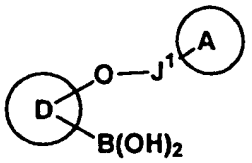


(VIII-B)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein the compound represented by general formula (XXIII) and the compound represented by the general formula (V) are subjected to the reaction same as in aforesaid (a-1), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Among compounds represented by general formula (XV), the compounds in which J is bonded to ring D via oxygen atom, in other words, the compounds represented by general formula (XV-B)



(XV-B)

(in the formula, all symbols have the same aforesaid meanings) can be produced by a process wherein the compound represented by general formula (XXIV) and the compound represented by the general formula (V) are subjected to the reaction same as in aforesaid (a-1), and in accordance with requirements, deprotecting reaction and/or cleavage reaction from resin is carried out.

The deprotecting reaction and cleavage reaction from resin are carried out by aforesaid processes.

Compounds represented by general formula (II)-(XXV) used other starting materials or reagents are well known by themselves or can be produced by combining well known methods, for example, processes described in Comprehensive Orgamic Transformatlons: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc, 1999).

As may be clear to a person skilled in the art, the reaction accompanied with heating in each reaction in this specification, can be carried out using water bath, oil bath, sand bath or a microwave.

In each reaction in this specification, a solid phase reagent supported on a high molecular weight polymer (for example polystyrene, polyacrylamide, polypropylene, polyethyleneglycol or the like) may be suitable used.

In each reaction in this specification, the reaction product can be purified by ordinary purification techniques, for example, distillation under reduced pressure or ambient pressure, high performance liquid chromatography using silica gel or magnesium silicate, thin layer chromatography, ion exchange resin, scavenger resin or column chromatography or processes such as washing, recrystallization or the like. The purification may be carried out after each reaction and may be carried out after completion of several reactions.

In the reaction using polystyrene resin in this specification, the reaction product can be purified by ordinary purification techniques, for example, washing several times with solvent (N,N-dimethylformamide, methylene chloride, methanol, tetrahydrofuran, toluene, acetic acid / toluene or the like).

[Pharmacological activity]

As pharmacological test other than described in the Examples, for example there are processes shown below. The CCR4 antagonism of the compounds of this invention can be shown in vitro using the process shown below, and moreover the effectiveness can be confirmed in vivo.

As system for screening CCR4 antagonist, for example because CCR4 is a G protein-coupled seven times of transmembrane type acceptor, the ligand of CCR4 other than MDC, for example a system wherein the effect of TARC and the like with respect to transient rise of Ca ion induced via CCR4 is measured, can be performed. Moreover, CCR4 antagonism can be demonstrated by processed described in WO2002/30357, WO2002/30358, WO2002/94264, or process in accordance with these, and aforesaid processes can be used as screening method. Moreover, in the patent applications exemplified here, experiment processes using animal are also described, and it is possible to confirm the effectiveness of CCR4 antagonist using in vivo model by aforesaid processes or processes in accordance with these.

[Toxicity].

Toxicity of the compounds of this invention is extremely low, and it can be assessed to be satisfactorily safe for the use as a drug.

Possible Applications in Industry

[Application to Drugs].

Because the compounds of this invention represented by general formula (I) have CCR4 antagonism in animals including man, in particular in human, it is thought to be useful as prevention and/or therapeutic agent with respect to diseases involving CCR4, in other words, CCR4-mediated diseases such as inflammation / allergic disease [for example systemic inflammatory response syndrome (SIRS), anaphylaxis or anaphylactoid reaction, allergic vasculitis, transplantation organ rejection, hepatitis, nephritis, nephropathy, pancreatitis, rhinitis, arthritis, inflammatory eye diseases (for example conjunctivitis or the like), inflammatory enteric disease (for example ulcerative colitis, Crohn disease, easinophilic gastroenteropathy or the like), brain / circulatory organ system diseases (for example arteriosclerosis, thrombosis, ischemia / reperfusion disorder, restenosis, infarction or the like) respiratory system disease (for example acute respiration distress syndrome [ARDS], asthema, allergic bronchopulmonary aspergillosis or the like), dermatosis (for example dermatitis (for example atopic dermatitis, psoriasis, contact dermatitis, eczema, urticaria, pruritus or the like), or the like), autoimmune disease (for example, multiple sclerosis, chronic rheumatism, systemic lupus erythematosus, type I diabetes mellitus, glomerulonephritis, Sjogren syndrome or the like)],

metabolism / endocrine system diseases [for example diabetes mellituses], cancerous disease [for example malignant neoplasm (for example, leukemia, cancer, metastatic cancer or the like), or the like], infection [for example viral disease (for example acquired immunodeficiency syndrome, SARS or the like) or the like].

Moreover, the compounds of this invention represented by general formula (I) have action to control the quantity of TNF alpha in vivo, in particular in blood, in other words, TNF alpha control action, in particular have TNF alpha production inhibitory action, and moreover have action to inhibit the function of effector cells expressing CCR4 (for example migration or the like), in other words, function inhibitory action of effector cells, therefore, it is considered to be useful as prevention and/or therapeutic agent for diseases in which the participation of TNF alpha is suggested and diseases in which the participation of effector cells is suggested, in particular aforesaid disease groups or the like.

The compounds of this invention represented by general formula (I) or non-toxic salts thereof can be combined with other agents for the purpose of
1) complementation and/or potentiation of prevention and/or therapeutic effect of the compound thereof,
2) improvement of dynamics / absorption or dose reduction of the compound thereof, and/or
3) relief of side effect of the compound thereof, and it may be administered as concomitant drug.

Moreover, the compounds of this invention are combined for the purpose of (1) complementation and/or potentiation of prevention and/or therapeutic effect of the concomitant drug, (2) improvement of dynamics / absorption or dose reduction of the concomitant drug, and/or (3) relief of side effect of the concomitant drug, and it may be administered as concomitant drug.

The concomitant drug of the compound represented by general formula (I) and other agent may be administered with a form of the compounding agent in which both components are formulated in a single formulation, and moreover with a form in which they are formulated separately and administered. When administered by separate formulations, the simultaneous administration and administration with time difference are included. Moreover, in the administration with time difference, the compound represented by general formula (I) is administered first, and the other agent is administered later, or the other agent is administered first and the compound represented by general formula (I) is administered later. The administration method of each may be the same or different.

The diseases which benefit from the prevention and/or therapeutic effect by aforesaid concomitant drug are not restricted in particular, as long as the diseases in which the prevention and/or therapeutic effect of the compound represented by general formula (I) is complemented and/or reinforced.

The weight ratio of compound represented by general formula (I) and the other agent is not restricted in particular.

As other agent, arbitrary two kinds or more species may be combined and administered.

Moreover, in other agents that complement and/or reinforce the prevention and/or therapeutic effect of the compound represented by general formula (I), the agents whch may be discovered in future are included in addition to the agents discovered to date based on aforesaid mechanism.

For example, as other agent to complement and/or reinforce the prevention and/or therapeutic effect of the compound represented by general formula (I) with respect to atopic dermatitis, for example steroid drug, non-steroial anti-inflammatory agent, immunosuppressive drug, prostaglandins, antiallergic drug, mediator release suppresser, antihistamine, metabolism promotion agent (forskolin formulation or the like), phosphodiesterase inhibitor, chemokine inhibitor and the like are nominated.

As other agent to complement and/or reinforce the prevention and/or therapeutic effect of the compounds of this invention represented by the general formula (I) with respect to allergic conjunctivitis, for example, leukotriene receptor antagonist, antihistamine, mediator release suppresser, non-steroidal anti-inflammatory agent, prostaglandins, steroid drug, nitric oxide synthase inhibitor, chemokine inhibitor and the like are nominated.

As other agent to complement and/or reinforce the prevention and/or therapeutic effect of the compounds of this invention represented by general formula (I) with respect to allergic rhinitis, for example, antihistamine, mediator release suppresser, thromboxane synthase inhibitor, thromboxane A2 receptor antagonist, leukotriene receptor antagonist, steroid drug, alpha adrenergic receptor irritant, xanthine derivative, anticholinergic, prostaglandins, nitric oxide synthase inhibitor, beta 2 adrenergic receptor irritant, phosphodiesterase inhibitor, chemokine inhibitor and the like are nominated.

As other agent to complement and/or reinforce the prevention and/or therapeutic effect of the compound represented by general formula (I) with respect to asthma, for example, bronchodilator (B2 adrenergic receptor irritant, xanthine derivative, anticholinergic or the like), anti-inflammatory agent (steroid drug, non-steroidal anti-inflammatory agent or the like), prostaglandins, leukotriene receptor antagonist, phosphodiesterase inhibitor, chemokine inhibitor, Chinese medicine and the like are nominated.

Astopical steroid drug, for example, clobetasol propionate, acetic acid diflorasone, fluocinonide, furancarboxylic acid mometazone, betamethasone propionate, butyric acid propionic acid betamethasone, betamethasone valerate, difluprednate, budesonide, diflucortolone propionate, amcinonide, halcinonide, dexamethasone, propionic acid dexamethasone, dexamethasone valerate, acetic acid dexamethasone, hydrocortisone acetate, hydrocortisone butyrate, butyric acid propionic acid hydrocortisone, deprodone propionate, valeric acid prednisolone acetate, fluocinolone acetonide, beclomethasone propionate, triamcinolone acetonide, flumethasone pivalate, alclomethasone propionate, clobetasone butyrate, prednisolone, beclomethasone propionate, fludroxycortide and the like are nominated.

As, oral medicine or injection, for example, cortisone acetate, hydrocortisone, phosphoric acid hydrocortisone sodium, succinic acid hydrocortisone sodium, acetic acid fludrocortisone, prednisolone, prednisolone acetate, succinic acid prednisolone sodium, butyl prednisolone acetate, phosphoric acid prednisolone sodium, halopredone, methyl prednisolone, methyl acetate prednisolone, succinic acid methyl prednisolone sodium, triamcinolone, acetic acid triamcinolone, triamcinolone acetonide, dexamethasone, acetic acid dexamethasone, phosphoric acid dexamethasone sodium, dexamethasone palmitate, paramethasone acetate, betamethasone and the like are nominated.

As inhalant, for example, beclomethasone propionate, fluticasone propionate, budesonide, flunisolide, triamcinolone, ST-126P, ciclesonide, dexamethasone palpitate, mometazone furan carbonate, prasterone sulfate, deflazacort, methylprednisolone suleptanate, methyl prednisolone sodium succinate and the like are nominated.

As non-steroid anti-inflammatory agent, for example, sasapyrine, sodium salicylate, aspirin, aspirin / dialuminate formulated, diflunisal, indomethacin, suprofen, ufenamate, dimethyl isopropyl azulene, bufexamax, felbinac, diclofenac, tolmetin sodium, clinoril, fenbufen, nabumetone, proglumetacin, indomethacin farnesyl, acemetacin, proglumetacin maleate, amfenac sodium, mofezolac, etodolac, ibuprofen, ibuprofen piconol, naproxen, flurbiprofen, flurbiprofen

axetil, ketoprofen, fenoprofen calcium, thiaprofen, oxaprozin, pranoprofen, loxoprofen sodium, alminoprofen, zaltoprofen, mefenamic acid, mefenamic acid aluminum, tolfenamic acid, floctafenine, ketophenylbutazone, oxyfenbutazone, piroxicam, tenoxicam, ampiroxicam, napageln ointment, epirizole, tiaramide hydrochloride, tinoridine hydrochloride, emorfazone, sulpyrine, Migrenin, Saridon, Sedes G, Amipylo-N, solvon(?), pyrine-series cold drug, acetaminophen, phenacetin, dimetotiazine mesylate, simetride compound, non-pyrine-series cold drug and the like are nominated.

As immunosuppressive drug, for example, proto pick (FK-506), methotrexate, cyclosporine, ascomycin, leflunomide, bucillamine, salazosulfapyridine, sirolimus, mycophenolate mofetil and the like are nominated.

As prostaglandins (hereinafter abbreviated to FG), PG receptor agonist, PG receptor antagonist and the like are nominated.

As PG receptor,PGE receptor (EP1, EP2, EPB, EP4), PGD receptor (DP, CRTH2), PGF receptor (FP), PGI receptor (IP), TX receptor (TP) and the like are nominated.

As mediator release suppresser, for example, tranilast, disodium cromoglycate, amlexanox, repirinast, ibudilast, tazanolast, pemirolast potassium and the like are nominated.

As antihistamine, for example, ketotifen fumarate, mequitazine, azelastine hydrochloride, oxatomide, terfenadine, Emedastine fumarate, epinastine hydrochloride, astemizole, ebastine, Cetirizine hydrochloride, Bepotastine, fexofenadine, loratadine, desloratadine, olopatadine hydrochloride, TAK-427, ZCR-2060, NIP-530, Mometasone furoate, Mizolastine, BP-294, andolast, auranofin, acrivastine, famotidine, ranitidine, cimetidine and the like are nominated.

As phosphodiesterase inhibitor, for example, rolipram which is PDE4 inhibitor, cilomilast (trade name Ariflo), Bay19-8004, NIK-616, roflumilast (BY-217), cipamfylline (BRL-61063), atizoram (CP-80633), SCH-351591, YM-976, V-11294A, PD-168787, D-4396, IC-485 and the like are nominated.

As leukotriene receptor antagonist, for example, Pranlukast hydrate, montelukast, zafirlukast, seratrodast, MCC-847, KCA-757, CS-615, YI) 4-158, L-740515, CP-195494, Lh4-1484, RS-635, A-93178, S-36496, BIIL-284, ONO-4057 and the like are nominated.

As thromboxane A2 receptor antagonist, for example, seratrodast, Ramatroban, Domitroban calcium hydrate, KT-2-962 and the like are nominated.

As thromboxane synthase inhibitor, for example, ozagrel hydrochloride, Imitrodast sodium and the like are nominated.

As xanthine derivative, for example, aminophylline, theophylline, doxophylline, cipamfylline, diprofylline and the like are nominated.

As anticholinergic, for example, ipratropium bromide, oxitropium bromide, flutropium bromide, cimetropium bromide, temivarine, thiotropium bromide, revatropate (UK-112166), oxybutinin hydrochloride bethanechol hydrochloride, propiverine hydrochloride, propantheline bromide, methylbenactyzium bromide, butylbromide scopolamine, Tolterodine tartrate, trospium chloride, Z-338, UK-112166-O4, KRP-197, darifenacin, YM-905, mepenzolate bromide, ipratropium bromide or the like are nominated.

As beta 2 adrenergic receptor stimulant, for example, hydrobromic acid fenoterol, salbutamol sulphate, terbutaline sulphate, formaterol fumarate, salmeterol xinafoate, isoproterenol sulphate, orciprenaline sulphate, clorprenaline sulphate, epinephrine, trimetoquinol hydrochloride, hexoprenaline sulphate, procaterol hydrochloride, tulobuterol hydrochloride, tulobuterol, pirbuterol hydrochloride, clenbuterol hydrochloride, mabuterol hydrochloride, ritodrine hydrochloride, banbuterol, dopexamine hydrochloride, meluadrine tartrate, AR-C68397, levosalbutamol, R,R-formaterol, KUR-1246, KUL-7211, AR-C89855, S-1319 and the like are nominated.

As chemokine inhibitor, endogenous ligands of chemokine receptor or derivatives thereof, and nonpeptide low molecular weight compounds or antibody with respect to chemokine receptor are included.

As endogenous ligand of chemokine receptor, for example, MIP-1alpha, MIP-1beta, RANTES, SDF-1alpha, SDF-1beta, MCP-1, MCP-2, MCP-4, eotaxin, MDC and the like are nominated.

As derivatives of endogenous ligand, for example, AOP-RANTES, Met-SDF-1 alpha, Met-SDF-1 beta and the like are nominated.

As antibody of chemokine receptor, for example, Pro-140 and the like are nominated.

As nonpeptide low molecular weight compound, for example, CCR1, CCR2, CCR3, CCR4, CCR5, CXCR1, CXCR2, CXCR3, CXCR4 receptor antagonists and agonists are nominated.

As Chinese medicine, for example, Sho-sei-ryu-to, Ma-ou-to, Bakuu-mon-tou-to and the like are nominated.

The compounds of this invention represented by general formula (I) have low toxicity and are safe, therefore, these can be administered for example to human and mammalian organisms other than human (for example rat, mouse, rabbit, sheep, pig, cattle, cat, dog, monkey or the like).

When the compounds of this invention represented by general formula (I), or pharmacologically permitted salt, acid addition salt or hydrate as the salt thereof or a concomitant drug of compound represented by as the general formula (I) and other agent is used for the aforesaid object, usually, it is administered sytemically or topically, in the form of orl or aoral route.

Dose differs depending on the age, body weight, symptom, therapy effect, administration method and treatment time, however, usually, for one adult, it is orally administered in a range of 1 ng to 100 mg per dosing, for once to several times per day, or for one adult, it is intravenously continuously administered in a range of 1 hour-24 hours per day.

Of course, because dose changes due to various kinds of conditions as described above, there may be a case wherein a smaller quantity than aforesaid dose is sufficient, or there may be a case wherein the administration beyond the range is required.

When the compounds of this invention represented by general formula (I) or concomitant drug of compound represented by general formula (I) and other agent is administered, it is used as solid agent for internal, liquid agent for internal use for the oral administration, or injection agent, topical agent, suppository, instillation, nasal drops, inhalant for aoral administration.

In the solid agent for internal use for oral administration, tablet, pill, encapsulated formulation, powder, granule and the like are included. In the encapsulated formulation, hard capsule and soft capsule are included.

In such solid agent for internal use, one or more active materials are used as thery are, or mixed with excipient (lactose, mannitol, glucose, microcrystalline cellulose, starch or the like), binding

agent (hydroxypropylcellulose, polyvinylpyrrolidone, magnesium metasilicate aluminate or the like), disintegrating agent (calcium carboxymethyl cellulose or the like), lubricant (magnesium stearate or the like), stabilizer, solubilizer (glutamic acid, aspartic acid and the like), and it is pharmaceutically formulated by normal methods, and used. Moreover, in accordance with requirements, it may be coated with coating agent (refined sugar, gelatin, hydroxypropylcellulose, hydroxypropyl methyl cellulose phthalate or the like), or it may be also coated in layers of more than 2. Furthermore, capsules of the substances which can be absorbed, such as gelatin, are included, too.

Liquid agent for internal use for oral administration includes pharmaceutically acceptable liquid agent, suspending agent, emulsion, syrup, elixir agent or the like. In such liquid agent, one or more active material is dissolved, suspended or emulsified in generally used diluent (purified water, ethanol or those mixed solution or the like). This liquid agent may further contain wetting agent, suspending agent, emulsifier, sweetener, flavor agent, aromatic, preservative, buffer agent or the like.

For example, in formulation of topical agent for aoral administration, ointment, gel agent, cream agent, pack agent, patch, liniment, propellant, inhalant, spray agent, aerosol, instillation and nasal drops and the like are included. These include one or more active material and can be prepared by well known methods or by conventionally-used formulations.

Ointment is produced by commonly known or conventionally-used formulations. For example, one or more active materials are triturated or melted into a base, and prepared. Ointment base is selected from commonly known or usually used species. Single species or two kinds or more selected from for example higher fatty acid or higher fatty acid ester (adipic acid, myristic acid, palmitic acid, stearic acid, oleic acid, adipate, myristate, palmitate, stearate, oleate or the like), wax species (beeswax, whale wax, ceresin or the like), detergent (polyoxyethylene alkylether phosphoester or the like), higher alcohol (cethanol, stearyl alcohol, cetostearyl alcohol or the like), silicone oil (dimethylpolysiloxane or the like), hydrocarbons (hydrophilicity vaseline, white petrolatum, purified lanolin, liquid paraffin or the like), glycol species (ethylene glycol, diethylene glycol, propylene glycol, polyethylene glycol, macrogol or the like), plant oil (castor oil, olive oil, sesami oil, terpentine oil or the like), animal oil (mink oil, egg yolk oil, squalane, squalene or the like), water, absorption promoter or anti-rash agent are mixed and used. Moreover, moisturizing agent, preservative, stabilising agent, anti-oxidant, flavouring agent or the like may be included.

Gel agent is produced by commonly known or conventionally-used formulations. For example, one or more active materials are melted in a base and is prepared. Gel base is selected from commonly known or usually used species. Single species or two kinds or more selected from for example lower alcohol (ethanol, isopropyl alcohol or the like), gelatinizer (carboxymethylcellulose, hydroxyethyl cellulose, hydroxy propyl cellulose, ethyl cellulose or the like), neutralizer (triethanolamine, diisopropanolamine or the like), detergent (monostearin acid polyethyleneglycol or the like), gum species, water, absorption promoter, or anti-rash agent are mixed and used. Moreover, preservative, anti-oxidant, flavouring agent or the like may be included.

Cream agent is produced by commonly known or conventionally-used formulations. For example, one or more active materials are melted or emulsified in a base, and prepared. Cream base is selected from commonly known or usually used species. Single species or two kinds or more selected from for example higher fatty acid ester, lower alcohol, hydrocarbons, polyvalent alcohol (propylene glycol, 1,3-butylene glycol or the like), higher alcohol (2-hexyl decanol, cethanol or the like), emulsifier (polyoxyethylene alkylether species, fatty acid ester species or the like), water, absorption promoter, or anti-rash agent are mixed and used. Moreover, preservative, anti-oxidant, flavouring agent or the like may be included.

Pack agent is produced by commonly known or conventionally-used formulations. For example, one or more active materials are melted in a base, and kneaded material is formed, and it is spread on a support, and it is produced. Pack base is selected from commonly known or usually used species. Single species or two kinds or more selected from for example thickener (polyacrylic acid, polyvinylpyrrolidone, gum arabic, starch, gelatin, methyl cellulose or the like), wetting agent (urea, glycerol, propylene glycol or the like), filler (kaolin, zinc oxide, talc, calcium, magnesium or the like), water, solubilizer, tackifier or anti-rash agent are mixed and used. Moreover, preservative, anti-oxidant, flavouring agent or the like may be included.

Patch is produced by commonly known or conventionally-used formulations. For example, one or more active materials are melted in a base, and it is spread on a support, and it is produced. Base for patch is selected from commonly known or usually used species. Single species or two kinds or more selected from for example polymer base, oils and fats, higher fatty acid, tackifier or anti-rash agent are mixed and used. Moreover, preservative, anti-oxidant, flavouring agent or the like may be included.

Liniment is produced by commonly known or conventionally-used formulations. For example,

one or more active materials are dissolved, suspended or emulsified in single species or two or more kinds selected from water, alcohol (ethanol, polyethyleneglycol or the like), higher fatty acid, glycerol, soap, emulsifier, suspending agent and it is prepared. Moreover, preservative, anti-oxidant, flavouring agent or the like may be included.

Aerosol, inhaler and spray agent may contain, in addition to generally used diluent, stabilizer such as sodium bisulfite, buffer agent which imparts isotonicity, for example, isotonizing agent such as sodium chloride, sodium citrate. A process for the production of spray agent is described in detail for example in US Patent No 2,868,691 and Ditto issue 3,095,355.

Injection agent for aoral administration includes all injection agents, drip infusion agent is also included. For example, injection agent to muslce, injection agent to subcutanous, injection agent to intracutanous, injection agent to intraarterial, injection agent to intraveous, injection agent to intraperitoneal, injection agent to intraspinal, drip infusion agent to intravenous or the like are included.

Injection agent for aoral administration includes solution, suspension, emulsion and solid injection agent which is dissolved or suspended in solvent at the time of use. Injection agent is used by dissolving, suspending or emulsifying one or more active materials in solvent.

As solvent, for example distilled water for injection, physiological saline, vegetable oil, an alcohol such as propylene glycol, polyethyleneglycol, ethanol and those combinations are used. This injection may further include stabilizer, solubilizer (glutamic acid, aspartic acid, polysorbate 80 [Registered Trade Name] or the like), suspending agent, emulsifier, analgesic, buffer agent, preservative or the like. These are prepared by sterilizing in the final step or by aseptic operation method. Moreover, sterile solid agent, for example lyophilization product is produced and it is dissolved in sterilized or sterile distilled water for injection or other solvent before use thereof and it can be used.

Instillations for aoal administration include eye drop liquid, suspension type eye drop liquid, emulsion type eye drop liquid, dissolution on use type eye drop liquid and eye ointment.

These instillations are prepared in accordance with well known methods. For example, one or more active materials are dissolved, suspended or emulsified in solvent and used. As solvent for instillation, for example, sterilized purified water, physiological saline, other aqueous solvent or injectable non-aqueous agent (for example vegetable oil or the like) and combination of these are

used. In accordance with requirements, the instillation may contain suitably selected isotonizing agent (sodium chloride, strong glycerol or the like), buffering agent (sodium phosphate, sodium acetate or the like), surface active agent (polysorbate 80 (trade name), stearic acid polyoxil 40, polyoxyethylene hardened castor oil or the like), stabilising agent (sodium citrate, sodium EDTA salt or the like), preservatives (benzalkonium chloride, paraben or the like) or the like. These may be sterilize in the final step or are prepared by aseptic operation method. Moreover, sterile solid agent, for example lyophilization product is produced and it is dissolved in sterilized or sterile purified water or other solvent before use thereof and it can be used.

As inhalant for parenteral administration, aerosol, powder agent for inhalation or liquid agent for inhalation are included and said liquid agent for aforesaid inhalation may be a form whcih is dissolves or suspended in water or other suitable vehicle at the time of use.

These inhalants are produced in accordance with well known methods.

For example, in the case of liquid agent for inhalation, preservatives (benzalkonium chloride, paraben or the like), colorant, buffering agent (sodium phosphate, sodium acetate or the like), isotonizing agent (sodium chloride, strong glycerol or the like), thickener (carboxy vinyl polymer or the like), absorption accelerating agent or the like are suitably selected in accordance with requirements, and it is prepared.

In the case of powder agent for inhalation, lubricant (stearic acid or salts thereof or the like), binding agent (starch, dextrin or the like), excipient (milk sugar, cellulose or the like), colorant, preservatives (benzalkonium chloride, paraben or the like), absorption accelerating agent or the like are s suitably elected in accordance with requirements, andit is prepared.

Nebulizer (atomizer, nebulizer) is usually used when administering liquid agent for inhalation, and inhalation administration device for powder agent is usually used when administering powder agent for inhalation.

As other compositions for aoral administration, suppository for rectal administration and pessary for intravaginal administration and the like which contain one or more active material and are formulated in accordance with conventional procedures are included.

The naming of the compounds of this invention is shown below.

The compound names used in this specification are named by a method in accordance with the rules of IUPAC, or named using a computer program, ACD/Name (Registered Trade Name, version 6.00, Advanced Chemistry Development Inc, Co.) which carries out naming in general in accordance with the rules of IUPAC.

Ideal form for Carrying Out the Invention

Hereinafter, this invention is explained in detail by Reference Examples and Examples. However, this invention is not restricted to these.

The solvent in brackets shown in the section of separation by chromatography and TLC shows the eluting solvent or developing solvent used, and the proportion shows the volume ratio.

The solvent in brackets shown in the section of NMR shows the solvent used in the measurement.

The MS was carried out using ESI method (electron spray ionization method) with detection of anion (Pos. 20 V) only, unless described in particular.

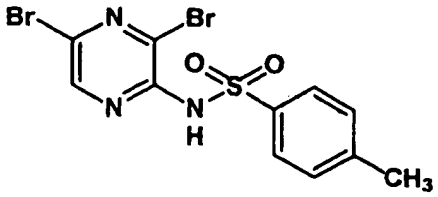
It was measured under the following condition, and measurement condition of HPLC was carried out so long as there was not description in particular.

Used column: Xtena (Registered Trade Name) MS C18 5 μm, 4.6 x 50 mm I.D.
Used flow rate: 3 m L/min.
Used solvent.
A liquid: 0.1 % trifluoroacetic acid aqueous solution
B liquid: 0.1 % trifluoroacetic acid-acetonitrile solution.

After the start of the measurement, the mixing proportion of A liquid and B liquid was fixed at 95/5 for 0.5 minutes. Thereafter, mixing proportion of A liquid and B liquid was changed linearly to 0/100 over 2.5 minutes. Thereafter, the mixing proportion of A liquid and B liquid was fixed at 0/100 for 0.5 minutes. Thereafter, the mixing proportion of A liquid and B liquid was changed to 95/5 linearly over 0.01 minute.

Reference Example 1

2,6-dibromo-3-(4-methylphenyl sulfonyl amino) pyrazine.



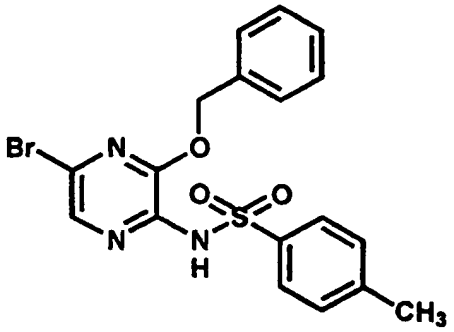
60 % sodium hydride (1 g) was added to 1,2-dimethoxyethane (20mL) solution of 2,6-dibromo-3-aminopyrazine (2.53 g) under ice cooling. Mixture was stirred at room temperature for 30 minutes. To the mixture was added p-toluenesulphonyl chloride (1.91 g) under ice cooling. The reaction mixture was stirred at 0°C for one hour 30 minutes. 2N hydrochloric acid was added to the reaction mixture, and it was concentrated. The aqueous layer was extracted with ethyl acetate. The extract was washed with saturated sodium chloride aqueous solution and dried with anhydrous magnesium sulphate, and concentration was carried out. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 5 : 1-2 : 1) and the title compound (2.04 g) having the following physical property values was obtained.

TLC : Rf 0.28 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 8.44 (s, 1H), 7.86 (d, J = 8.1Hz, 2H), 7.38 (d, J = 8.1Hz, 2H), 2.37 (s, 3H).

Example 1

6-bromo-2-(phenylmethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.



60 % sodium hydride (118 mg) was added at room temperature to 1,4-dioxane (3mL) solution of benzyl alcohol (0.153mL). Mixture was stirred at room temperature for 30 minutes, and compound (300 mg) produced in Reference Example 1 was added. The reaction mixture was stirred at 65°C for one hour 30 minutes. 1N hydrochloric acid was added to the reaction mixture, and it was concentrated. The aqueous layer was extracted with ethyl acetate. The extract was washed with saturated sodium chloride aqueous solution and dried with anhydrous magnesium sulphate, and concentration was carried out. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 6 : 1) and the compound of this invention

(305 mg) having the following physical property values was obtained.

TLC : Rf 0.57 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 11.12 (s, 1H), 7.92 (s, 1H), 7.85 (dd, J = 6.6, 1.8Hz 2H), 7.52 (dd, J = 6.6, 1.8 Hz, 2H), 7.43-7.34 (m, 5H), 5.36 (s, 2H), 2.35 (s, 3H).

Examples 1 (1)-1 (8)

The same procedures as in Example 1 was carried out using the alcohol derivative corresponding to benzyl alcohol and the compound produced in Reference Example 1, and the compounds of this invention shown below were obtained.

Example 1 (1)

6-bromo-2-((pyridine-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.59 (chloroform : methanol = 10 : 1);

NMR (d6-DMSO): δ 11.15 (br, 1H), 8.77 (d, J = 1.8Hz, 1H), 8.57 (dd, J = 5.1, 1.8Hz, 1H), 7.97-7.94 (m, 2H), 7.84 (d, J = 8.1Hz, 2H), 7.45 (dd, J = 7.8, 4.8Hz, 1H), 7.36 (d, J = 8.1Hz, 2H), 5.39 (s, 2H), 2.35 (s, 3H).

Example 1 (2)

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.47 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 11.06 (br, 1H), 7.91 (s, 1H), 7.84 (d, J = 8-4Hz, 2H), 7.35 (d, J = 8.4Hz, 2H), 7.15 (d, J = 1.8Hz, 1H), 7.04 (dd, J = 8.1, 1.8Hz, 1H), 6.95 (d, J = 8.1Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.35 (s, 3H).

Example 1 (3)

6-bromo-2-((3-(2-dimethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC = Rf 0.32 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.67 (d, J = 8.1Hz, 2H), 7.47 (s, 1H), 7.19 (d, J = 1.8Hz, 1H), 7.16 (d, J = 8.1Hz, 2H), 7.09 (dd, J = 8.1, 1.8Hz, 1H), 7.01 (d, J = 8.1Hz, 1H), 5.13 (s, 2H), 4.22 (t, J = 5.4Hz, 2H), 3.77 (s, 3H), 3.24 (t, J = 5.4Hz, 2H), 2.69 (s, 6H), 2.29 (s, 3H).

Example 1 (4)

6-bromo-2-((3-(2-[morpholine-4-yl] ethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.55 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 7.80 (m, 3H), 7.31 (d, J = 8.4Hz, 2H), 7.18 (d, J = 1.8Hz, 1H), 7.05 (dd, J = 8.1, 1.8Hz, 1H), 6.97 (d, J = 8.1Hz, 1H), 5.24 (s, 2H), 4.11 (t, J = 5.1Hz, 2H), 3.76 (s, 3H), 3.59 (m, 4H), 2.82 (t, J = 5.1Hz, 2H), 2.61 (m, 4H), 2.34 (s, 3H).

Example 1 (5)

6-bromo-2-((3-(2-diethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.33 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.67 (d, J = 7.5Hz, 2H), 7.47 (s, 1H), 7.19 (brs, 1H), 7.16 (d, J = 7.5Hz, 2H), 7.09 (brd, J = 7.2Hz, 1H), 7.01 (d, J = 7.2Hz, 1H), 5.14 (s, 2H), 4.25 (t, J = 5.1Hz, 2H), 3.78 (s, 3H), 3.38 (m, 2H), 3.12 (q, J = 7.2Hz, 4H), 2.29 (s, 3H), 1.18 (t, J = 7.2Hz, 6H).

Example 1 (6)

6-bromo-2-((3-(2-diisopropylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.43 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.68 (d, J = 8.1Hz, 2H), 7.51 (br, 1H), 7.19-7.15 (m, 3H), 7.05 (d, J = 8.1Hz, 1H), 6.98 (d, J = 8.1Hz, 1H), 5.16 (s, 2H), 4.12 (m, 2H), 3.76 (s, 3H), 3.60-3.30 (m, 4H), 2.29 (s, 3H), 1.21 (m, 12H).

Example 1 (7)

6-bromo-2-((3-(2-(N-methyl-N-[2-dimethylaminoethyl] amino) ethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine • triethylamine salt.

TLC : Rf 0.45 (chloroform : methanol : triethylamine = 9 : 1 : 0.5).

NMR (d6-DMSO): δ 7.63 (d, J = 7.8Hz, 2H), 7.36 (s, 1H) 7.12 (m, 3H), 7.01 (d, J = 7.8Hz, 1H), 6.95 (d, J = 7.8Hz, 1H), 5.10 (s, 2H), 4.09 (t, J = 5.4Hz, 2H), 3.75 (s, 3H), 2.95 (m, 8H), 2.80 (t, J = 5.4Hz, 2H), 2.70 (t, J = 6.0Hz, 2H), 2.59 (s, 6H), 2.31 (s, 3H), 2.27 (s, 3H), 1.12 (t, J = 7.5Hz, 9H).

Example 1 (8)

6-bromo-2-((3-dimethylaminomethyl-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.17 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.73 (d, J = 7.8Hz, 2H), 7.65 (s, 1H), 7.59 (dd, J = 8.7, 1.8Hz, 1H), 7.53 (d, J = 1.8Hz, 1H), 7.24 (d, J = 7.8Hz, 2H), 7.15 (d, J = 8.7Hz, 1H), 5.23 (s, 2H), 4.18 (s, 2H), 3.85 (s, 3H), 2.69 (s, 6H), 2.31 (s, 3H).

Example 2

5,6-dimethyl-2-((3-(2-dimethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

The same operation as in Reference Example 1 to Example 1 was carried out using 2-bromo-3-amino-5,6-dimethylpyrazine instead of 2,6-dibromo-3-aminopyrazine and 3-(2-dimethylaminoethyl) oxy-4-methoxybenzyl alcohol instead of benzyl alcohol, and the compound of this invention having the following physical property values was obtained.

TLC = Rf 0.30 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 7.85 (d, J = 8.4Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 2.1Hz, 1H), 7.02 (dd, J = 8.4, 2.1Hz, 1H), 6.93 (d, J = 8.4Hz, 1H), 5.21 (s, 2H), 4.05 (t, J = 6.0Hz, 2H), 3.74 (s, 3H), 2.72 (t, J = 6.0Hz, 2H), 2.34 (s, 3H), 2.29 (s, 6H), 2.24 (s, 3H), 2.18 (s, 3H).

Examples 2 (1)-2 (5)

Instead of 2-bromo-3-amino-5,6-dimethylpyrazine, corresponding pyrazines and instead of 3-(2-dimethylaminoethyl) oxy-4-methoxybenzyl alcohol, corresponding alcohol derivative were used and the same operation as in Example 2 was carried out, and the compounds of this invention shown below were obtained.

Example 2 (1)

6-methyl-2-((3-(2-[morpholine-4-yl] ethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC = Rf 0.58 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 7.85 (d, J = 8.4Hz, 2H), 7.52 (s, 1H), 7.27 (d, J = 8.4Hz, 2H), 7.13 (d, J = 1.8Hz, 1H), 7.00 (dd, J = 8.1, 1.8Hz, 1H), 6.92 (d, J = 8.1Hz, 1H), 5.33 (s, 2H), 4.16 (t, J = 5.7Hz, 2H), 3.82 (s, 3H), 3.69 (m, 4H), 2.81 (t, J= 5.7 Hz, 2H), 2.62 (m, 4H), 2.37 (s, 3H), 2.29 (s, 3H).

Example 2 (2)

6-methyl-2-((3-(2-diethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.33 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 7.78 (d, J = 8.1Hz, 2H), 7.50 (s, 1H), 7.28 (d, J = 8.1Hz, 2H), 7.15 (s, 1H), 7.04 (d, J = 8-1Hz, 1H), 6.95 (d, J = 8.1Hz, 1H), 5.23 (s, 2H), 4.05 (t, J = 6.0Hz, 2H), 3.75 (s, 3H), 2.93 (t, J = 6.0Hz, 2H), 2.69 (q, J = 7.2HC, 4H), 2.33 (s, 3H), 2.23 (s, 3H), 1.01 (t, J = 7.2Hz, 6H).

Example 2 (3)

6-methyl-2-((3-(2-diisopropylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.43 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.79 (d, J = 8.1Hz, 2H), 7.53 (s, 1H), 7.29 (d, J = 8.1Hz, 2H), 7.12 (s, 1H), 7.02 (d, J = 8.1Hz, 1H), 6.93 (d, J = 8.1Hz, 1H), 5.24 (s, 2H), 3.89 (t, J = 6.9Hz, 2H), 3.74 (s, 3H), 3.08 (m, 2H), 2.86 (t, J = 6.9Hz, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 1.00 (d, J = 6.3Hz, 12H).

Example 2 (4)

6-methyl-2-((3-(2-(N-methyl-N-[2-dimethylaminoethyl] amino) ethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine•triethylamine salt.

TLC = Rf 0.45 (chloroform : methanol : triethylamine = 9 : 1 : 0.5).

NMR (d6-DMSO): δ 7.75 (d, J = 8.1Hz, 2H), 7.43 (s, 1H), 7.24 (d, J = 8.1Hz, 2H), 7.15 (Ss, 1H), 7.03 (d, J = 8.1Hz, 1H), 6.95 (d, J = 8.1Hz, 1H), 5.21 (s, 2H), 4.08 (t, J = 5.1Hz, 2H), 3.75 (s, 3H), 2.96 (q, J = 7.2Hz, 6H), 2.88 (t, J = 6.0Hz, 2H), 2.79 (t, J = 5.1Hz, 2H), 2.68 (t, J = 6.0Hz, 2H), 2.54 (s, 6H), 2.31 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 1.13 (t, J = 7.2Hz, 9H).

Example 2 (5)

6-methyl-2-((3-dimethylaminomethyl-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC = Rf 0.17 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.79 (d, J = 8.4Hz, 2H), 7.53 (s, 1H), 7.46 (m, 2H), 7.30 (d, J = 8.4Hz, 2H), 7.04 (d, J= 9.0Hz, 1H), 5.27 (s, 2H), 3.80 (s, 3H), 3.71 (s, 2H), 2.37 (s, 6H), 2.33 (s, 3H), 2.24 (s, 3H).

Reference Example 2

2-chloro-3-(4-methylphenyl sulfonyl amino) pyrazinePotassium carbonate (13.91 g) was added to dimethylsulfoxide (60 mL) solution of 2,3-dichloro pyrazine (5 g) and 4-methylbenzene sulfonamide (5.74 g). The reaction mixture was stirred at 110°C for four hours. The reaction mixture was cooled to room temperature, and water and 2N hydrochloric acid were added. Precipitated solid was filtered and dried, and the title compound having the following physical property values (7.67 g) was obtained.

TLC: Rf 0.74 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 11.19 (br, 1H), 8.22 (d, J = 2.4Hz, 1H), 8.11 (d, J = 2.4Hz, 1H), 7.88 (d, J = 8.4Hz, 2H), 7.38 (d, J = 8.4Hz, 2H), 2.37 (s, 3H).

Example 3

2-[phenylmethyl oxy]-3-(4-methylphenyl sulfonyl amino) pyrazine Using the compound produced in Reference Example 2 instead of the compound produced in Reference Example 1, the same procedures as in Example 1 was carried out and the compound of this invention having the following physical property values was obtained.

TLC = Rf 0.38 (hexane : ethyl acetate = 2 : 1).

NMR (d6-DMSO): δ 10.91 (brs, 1H), 7.87 (d, J = 8.1Hz, 2H), 7.73 (m, 2H), 7.50 (m, 2H), 7.36 (m, 5H), 5.38 (s, 2H), 2.35 (s, 3H).

Examples 3 (1)-3 (11)

Instead of benzyl alcohol and the compound produced in Reference Example 2, using the corresponding alcohol derivative, the same operation as in Example 3 was carried out, and the compounds of this invention shown below were obtained.

Example 3 (1)

2-((pyridine-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.43 (chloroform : methanol = 10 : 1);

NMR (d6-DMSO): δ 10.95 (s, 1H), 8.74 (d, J = 1.8Hz, 1H), 8.54 (dd, J = 4.8, 1.8Hz, 1H), 7.92 (d, J = 7.8Hz, 1H), 7.85 (d, J = 8.4Hz, 2H), 7.75 (d, 3.0Hz, 1H), 7.73 (d, J = 3.0Hz, 1H), 7.41 (dd, J = 7.8, 4.8Hz, 1H), 7.35 (d, J = 8.4Hz, 2H), 5.40 (s, 2H), 2.34 (s, 3H).

Example 3 (2)

2-(2-phenoxy ethyl oxy]-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.62 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 10.88 (s, 1H), 7.86 (d, J = 8.4Hz, 2H), 7.71 (m, 2H), 7.34 (d, J = 8.4Hz, 2H), 7.29 (dd, J = 7.8, 7.2Hz, 2H), 6.97 (d, J = 7.8Hz, 2H), 6.94 (t, J = 7.2Hz, 1H), 4.60 (m, 2H), 4.34 (m, 2H), 2.34 (s, 3H).

Example 3 (3)

2-((pyridine-4-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC = Rf 0.35 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 11.04 (s, 1H), 8.56 (d, J = 5.7Hz, 2H), 7.88 (d, J = 8.4Hz, 2H), 7.74 (d, J = 2.7Hz, 1H), 7.72 (d, J = 2.7Hz, 1H), 7.49 (d, J = 5.7Hz, 2H), 7.36 (d, J = 8.4Hz, 2H), 5.43 (s, 2H), 2.35 (s, 3H).

Example 3 (4)

2-((3-methoxymethyl oxy phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.67 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 10.91 (s, 1H), 7.86 (d, J = 8.4Hz, 2H), 7.82-7.64 (m, 2H), 7.35 (d, J = 8.4Hz, 2H), 7.29 (t, J = 7.8Hz, 1H), 7.17 (brs, 1H), 7.11 (brd, J = 7.8Hz, 1H), 6.98 (m, 1H), 5.34 (s, 2H), 5.10 (s, 2H), 3.36 (s, 3H), 2.34 (s, 3H).

Example 3 (5)2-(3-aminophenyl methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.TLC : Rf 0.56 (benzene : ethyl acetate = 1 : 1). NMR (d6-DMSO): δ 7.88 (d, J = 8.1Hz, 2H), 7.74 (d, J = 3.0Hz, 1H), 7.71 (d, J = 3.0Hz, 1H), 7.36 (d, J = 8.1Hz, 2H), 7.01 (t, J = 7.2Hz, 1H), 6.63-6.61 (m, 2H), 6.57 (d, J = 7.2Hz, 1H), 5.24 (s, 2H), 2.36 (s, 3H).

Example 3 (6)

2-((3-(2-dimethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.27 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.78 (d, J = 8.4Hz, 2H), 7.54 (d, J = 3.0Hz, 1H), 7.49 (d, J = 3.0Hz, 1H), 7.26 (d, J = 8.4Hz, 2H), 7.14 (d, J = 1.5Hz, 1H), 7.04 (dd, J = 8.4, 1.5Hz, 1H), 6.96 (d, J = 8.4Hz, 1H), 5.23 (s, 2H), 4.11 (t, J = 5.4Hz, 2H), 3.75 (s, 3H), 2.91 (t, J = 5.4 Hz, 2H), 2.43 (s, 6H), 2.32 (s, 3H).

Example 3 (7)

2-((3-(2-[morpholine-4-yl] ethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.54 (chloroform : methanol = 10 : 1).

NMR (CD3OD): δ 7.99 (d, J = 7.8Hz, 2H), 7.64 (d, J = 3.0Hz, 1H), 7.62 (d, J = 3.0Hz, 1H), 7.29 (d, J = 7.8Hz, 2H), 7.14 (d, J = 2.1Hz, 1H), 7.02 (dd, J = 8.4, 2.1Hz, 1H), 6.93 (d, J = 8.4Hz, 1H), 5.35 (s, 2H), 4.16 (t, J = 5.4Hz, 2H), 3.82 (s, 3H), 3.70 (m, 4H), 2.82 (t, J = 5.4Hz, 2H), 2.64 (m, 4H), 2.38 (s, 3H).

Example 3 (8)

2-((3-(2-diethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.33 (chloroform : methanol = 10 : 1);

NMR (d6-DMSO): δ 7.78 (d, J = 8.1Hz, 2H), 7.53 (d, J = 2.7Hz, 1H), 7.47 (d, J = 2.7Hz, 1H), 7.25 (d, J = 8.1Hz, 2H), 7.14 (d, J = 1.2Hz, 1H), 7.04 (dd, J = 8.1, 1.2Hz, 1H), 6.96 (d, J = 8.1Hz,

1H), 5.23 (s, 2H), 4.12 (t, J = 6.0Hz, 2H), 3.75 (s, 3H), 3.08 (t, J = 6.0Hz, 2H), 2.84 (q, J = 6.9Hz, 4H), 2.32 (s, 3H), 1.07 (t, J = 6.9Hz, 6H).

Example 3 (9)

2-((3-(2-diisopropylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

TLC: Rf 0.43 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 7.81 (d, J = 8.1Hz, 2H), 7.60 (m, 2H), 7.29 (d, J = 8.1Hz, 2H), 7.12 (d, J = 1.5Hz, 1H), 7.03 (dd, J = 8.1, 1.5Hz, 1H), 6.95 (d, J = 8.1Hz, 1H), 5.26 (s, 2H), 3.98 (m, 2H), 3.75 (s, 3H), 3.36(m, 2H), 3.03 (br, 2H), 2.33 (s, 3H), 1.08 (d, J = 7.2Hz, 2H).

Example 3 (10)

2-((3-(2-(N-methyl-N-[2-dimethylaminoethyl] amino) ethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine • triethylamine salt.

TLC: Rf 0.45 (chloroform : methanol : triethylamine = 9 : 1 : 0.5).

NMR (d6-DMSO): δ 7.71 (d, J = 7.8Hz, 2H), 7.39 (d, J = 2.7Hz, 1H), 7.25 (d, J = 2.7Hz, 1H), 7.18 (d, J = 7.8Hz, 2H), 7.12 (s, 1H), 7.00 (d, J = 8.1Hz, 1H), 6.97 (d, J = 8.1Hz, 1H), 5.18 (s, 2H), 4.08 (t, J = 5.7Hz, 2H), 3.74 (s, 3H), 2.97 (m, 8H), 2.79 (t, J = 5.4Hz, 2H), 2.71(t, J= 5.7Hz, 2H), 2.60 (s, 6H), 2.31 (s, 3H), 2.29 (s, 3H), 1.14 (t, J = 7.2Hz, 9H).

Example 3 (11)

2-((3-dimethylaminomethyl-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.17 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 7.79 (d, J = 7.8Hz, 2H), 7.55 (d, J = 2.7Hz, 1H), 7.51 (d, J = 2.7Hz, 1H), 7.47 (s, 2H), 7.26 (d, J = 7.8Hz, 2H), 7.06 (d, J = 9.3Hz, 1H), 5.26 (s, 2H), 3.85 (s, 2H), 3.81 (s, 3H), 2.46 (s, 6H), 2.32 (s, 3H).

Example 4

2-((pyridine-3-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

The same operations as in Reference Example 2 to Example 1 were carried out using Instead of 4-chlorobenzenesulphonamide and 3-(hydroxymethyl) pyridine instead of 4-methylbenzene sulfonamide and benzyl alcohol respectivelly, and the compound of this invention having the following physical property values was obtained.

TLC : Rf 0.40 (hexane : ethyl acetate = 3 : 7)

NMR (d6-DMSO): δ 11.17 (s, 1H), 8.74 (d, J = 1.8Hz, 1H), 8.54 (dd, J = 4.8, 1.8Hz, 1H), 7.97 (d, J = 8.4Hz, 2H), 7.92 (d, J = 8.1Hz, 1H), 7.79 (d, J = 3.0Hz, 1H), 7.74 (d, J = 3.0Hz, 1H), 7.64 (d, J = 8.4Hz, 2H), 7.42 (dd, J = 8.1, 4.8Hz, 1H), 5.41 (s, 2H).

Examples 4 (1)-4 (5)

Instead of 4-chlorobenzenesulphonamide and 3-[hydroxymethyl] pyridine, using the corresponding sulfonamide derivative and the corresponding alcohol derivative respectivelly, the same operation as in Example 4 was carried out, and the compounds of this invention having the following physical property values were obtained.

Example 4 (1)

2-(2-phenoxy ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

TLC : Rf 0.68 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 11.11 (s, 1H), 7.97 (d, J = 8.4Hz, 2H), 7.76 (m, 1H), 7.72 (m, 1H), 7.63 (d, J = 8.4Hz, 2H), 7.29 (dd, J = 8.1, 7.2Hz, 2H), 6.97 (d, J = 8.1Hz, 2H), 6.94 (t, J= 7.2Hz, 1H), 4.61 (m, 2H), 4.34 (m, 2H).

Example 4 (2)

2-((pyridine-3-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

TLC: Rf 0.21 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 11.10 (s, 1H), 8.75 (d, J = 2.1Hz, 1H), 8.55 (dd, J = 4.5, 2.1Hz, 1H), 8.05 (dd, J = 7.2, 5.1Hz, 2H), 7.93 (m, 1H), 7.79 (d, J = 3.0Hz, 1H), 7.75 (d, J = 3.0Hz, 1H), 7.50-7.35 (m, 3H), 5.42 (s, 2H).

Example 4 (3)

2-(2-phenoxy ethyl oxy]-3-(4-fluorophenyl sulfonyl amino) pyrazine.

TLC = Rf 0.33 (hexane : ethyl acetate = 3 : 1)

NMR (d6-DMSO): δ 11.04 (s, 1H), 8.04 (m, 2H), 7.75 (m, 1H), 7.72 (m, 1H), 7.39 (t, J = 8.7Hz, 2H), 7.29 (t, J= 8.7Hz, 2H), 6.97 (d, J = 7.5Hz, 2H), 6.92 (d, J = 7.2Hz, 1H), 4.61 (m, 2H), 4.34 (m, 2H).

Example 4 (4)

2-((pyridine-3-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.40 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 10.95 (s, 1H), 8.74 (d, J = 1.8Hz, 1H), 8.54 (dd, J = 4.8, 1.8Hz, 1H), 7.93 (dt, J = 8.1, 1.8Hz, 1H), 7.89 (d, J = 8.4Hz, 2H), 7.76 (d, J = 3.0Hz, 1H), 7.74 (d, J = 3.0Hz, 1H),

7.42 (dd, J = 8.1, 4.8Hz, 1H), 7.38 (d, J = 8.4Hz, 2H), 5.40 (s, 2H), 2.65 (q, J= 7.5Hz, 2H), 1.16 (t, J = 7.5Hz, 3H).

Example 4 (5)

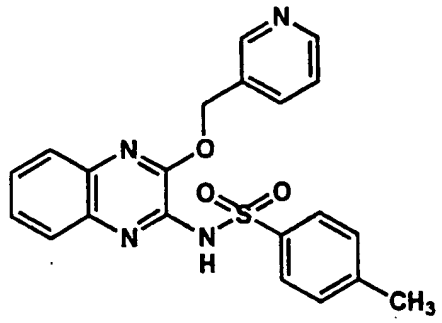
2-[phenylmethyl oxy]-3-(2-methoxy-4-methylphenyl sulfonyl amino) pyrazine.

TLC = Rf 0.59 (hexane : ethyl acetate = 1 : 1)

NMR ($CDCl_3$): δ 7.98 (d, J = 8.1Hz, 1H), 7.96 (s, 1H), 7.68 (d, J = 3.0Hz, 1H), 7.63 (d, J = 3.0Hz, 1H), 7.44-7.40 (m, 5H), 6.86 (d, J = 8.1Hz, 1H), 6.66 (s, 1H), 5.40 (s, 2H), 3.72 (s, 3H), 2.36 (s, 3H).

Example 5

2-((pyridine-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.



The same operations as in Reference Example 2 to Example 1 were carried out using 2,3-dichloroquinoxaline and 3-(hydroxymethyl) pyridine instead of 2,3-dichloro pyrazine and benzyl alcohol respectivelly, the compound of this invention having the following physical property values was obtained.

TLC : Rf 0.22 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 11.39 (brs, 1H), 8.84 (d, J = 1.8Hz, 1H), 8.58 (dd, J = 4.5, 1.8 Hz, 1H), 8.06 (d, J = 8.1Hz, 2H), 8.02 (m, 1H), 7.80-7.65 (m, 2H), 7.58-7.50 (m, 2H), 7.46 (m, 1H), 7.40 (d, J= 8.1 Hz, 2H), 5.57 (s, 2H), 2.35 (s, 3H).

Examples 5 (1)-5 (17)

Instead of 2,3-dichloroquinoxaline derivative or corresponding pyrazine derivative, 4-methylbenzene sulfonamide, using sulfonamide derivative, and instead of benzyl alcohol, using 3-[hydroxymethyl] pyridine, the same operation as in Example 5 was carried out and the compounds of this invention shown below were obtained.

Example 5 (1)

2-(2-phenoxy ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

TLC: Rf 0.71 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 11.30 (br, 1H), 8.05 (m, 2H), 7.70 (m, 2H), 7.50 (m, 2H), 7.40-7-28 (m, 4H), 7.01-6.95 (m, 3H), 4.75 (m, 2H), 4.43 (m, 2H), 2.33 (s, 3H).

Example 5 (2)

2-((pyridine-4-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

TLC: Rf 0.51 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 11.46 (br, 1H), 8.60 (m, 2H), 8.06 (m, 2H), 7.73 (m, 1H), 7.65 (m, 1H), 7.59 (m, 2H), 7.52 (m, 2H), 7.40 (m, 2H), 5.59 (s, 2H), 2.34 (s, 3H).

Example 5 (3)

2-((pyridine-3-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.15 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 12.00-11.00 (br, 1H), 8.82 (d, J = 1.8Hz, 1H), 8.56 (dd, J = 4.8, 1.8Hz, 1H), 8.14 (d, J = 8.4Hz, 2H), 8.01 (dt, J = 6.0, 1.8Hz, 1H), 7.72 (m, 2H), 7.67 (d, J = 8.4Hz, 2H), 7.53 (m, 2H), 7.44 (m, 1H) 5.55 (s, 2H).

Example 5 (4)

2-(2-phenoxy ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.83 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 11.50 (brs, 1H), 8.20-8.10 (m, 2H), 7.80-7.70 (m, 2H), 7.67 (d, J = 7.8Hz, 2H) 7.52 (m, 2H), 7.29 (t, J = 7.8Hz, 2H), 6.99 (d, J = 7.8Hz, 2H), 6.94 (t, J = 7.2Hz, 1H), 4.75 (m, 2H), 4.42 (m, 2H).

Example 5 (5)

2-((pyridine-4-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.12 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 8.58 (m, 2H), 8.13 (d, J = 8.4Hz, 2H), 7.70-7.57 (m, 4H), 7.55 (d, J = 5.7Hz, 2H), 7.45 (m, 2H), 5.55 (s, 2H).

Example 5 (6)

2-((pyridine-3-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

TLC: Rf 0.15 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 11.50 (brs, 1H), 8.82 (d, J = 1.8Hz, 1H), 8.56 (dd, J = 4.5, 1.8 Hz, 1H), 8.21 (m, 2H), 8.01 (dt, J = 7.8, 1.8Hz, 1H), 7.78-7.66 (m, 2H), 7.52 (m, 2H), 7.45 (m, 1H), 7.41 (m, 2H), 5.55 (s, 2H).

Example 5 (7)

2-(2-phenoxy ethyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline

TLC : Rf 0.71 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 11.41 (brs, 1H), 8.22 (m, 2H), 7.73 (m, 1H), 7.67 (m, 1H), 7.52 (m, 2H), 7.43 (t, J = 8.7Hz, 2H), 7.30 (dd, J = 8.7, 7.5Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 6.94 (t, J = 7.5Hz, 1H), 4.75 (m, 2H), 4.42(m, 2H).

Example 5 (8)

2-((pyridine-4-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

TLC: Rf 0.10 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 8.59 (m, 2H), 8.24 (m, 2H), 7.75 (m, 1H), 7.65 (m, 1H), 7.58 (m, 2H), 7.51 (m, 2H), 7.44 (m, 2H), 5.57 (s, 2H).

Example 5 (9)

2-((pyridine-3-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.18 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 11.40 (brs, 1H), 8.82 (d, J = 1.5Hz, 1H), 8.56 (dd, J = 4.8, 1.5Hz, 1H), 8.06 (d, J = 8.4Hz, 2H), 8.01 (m, 1H), 7.80-7.65 (m, 2H), 7.60-7.48 (m, 2H), 7.44 (m, 1H), 7.42 (d, J = 8.4Hz, 2H), 5.55 (s, 2H), 2.63 (q, J = 7.2Hz, 2H), 1.14(t, J = 7.2Hz, 3H).

Example 5 (10)

2-(2-phenoxy ethyl oxy]-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.76 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 11.28 (s, 1H), 8.07 (d, J = 8.4Hz, 2H), 7.71 (m, 1H), 7.66 (m, 1H), 7.51 (m, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 8.1, 7.2Hz, 2H), 6.99 (d, J = 8.1Hz, 2H), 6.94 (t, J = 7.2Hz, 1H), 4.74 (m, 2H), 4.42 (m, 2H), 2.63 (q, J = 7.5Hz, 2H), 1.14 (t, J = 7.5Hz, 3H).

Example 5 (11)

2-((pyridine-4-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.10 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 8.59 (m, 2H) 8.08 (d, J = 8.1Hz, 2H), 7.74 (m, 1H), 7.65 (m, 1H), 7.59 (d, J = 5.7Hz, 2H), 7.51 (m, 2H), 7.43 (d, J = 8.1Hz, 2H), 5.58 (s, 2H) 2.64 (q, J = 7.5Hz, 2H), 1.15 (t, J = 7.5Hz, 3H).

Example 5 (12)

2-[phenylmethyl oxy]-3-(4-methylphenyl sulfonyl amino) quinoxaline.

TLC : Rf 0.71 (hexane : ethyl acetate = 1 : 1).

NMR (d6-DMSO): δ 11.27 (s, 1H), 8.04 (d, J = 7.8Hz, 2H), 7.68 (m, 2H), 7.58 (d, J = 6.9Hz, 2H), 7.51 (m, 2H), 7.44-7.28 (m, 5H), 5.52 (s, 2H), 2.33 (s, 3H).

Example 5 (13)

2-((pyridine-3-yl) methyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

TLC : Rf 0.49 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO): δ 11.36 (brs, 1H), 8.83 (d, J = 1.5Hz, 1H), 8.56 (dd, J = 4.5, 1.5Hz, 1H), 8.06 (d, J = 8.4Hz, 2H), 8.01 (d, J = 4.5Hz, 1H), 7.69 (m, 2H), 7.52 (m, 2H), 7.44 (m, 1H), 7.40 (d, J = 8.4Hz, 2H), 5.55 (s, 2H), 2.59 (t, J = 7.5Hz, 2H), 1.55 (q, J = 7.5Hz, 2H), 0.84 (t, J = 7.5Hz, 3H).

Example 5 (14)

6-phenyl-2-((pyridine-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC: Rf 0.30 (hexane : ethyl acetate = 1 : 2)

NMR (d6-DMSO): δ 11.05 (brs, 1H), 8.82 (d, J = 2.1Hz, 1H), 8.54 (dd, J = 3.9, 2.1Hz, 1H), 8.37 (s, 1H), 7.99 (dd, J = 3.9, 1.8Hz, 3H), 7.89 (d, J = 8.1Hz, 2H), 7.45-7.36 (m, 6H), 5.56 (s, 2H), 2.35 (s, 3H).

Example 5 (15)

5-phenyl-2-((pyridine-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.29 (hexane : ethyl acetate = 1 : 2)

NMR (d6-DMSO): δ 11.14 (brs, 1H), 8.79 (m, 1H), 8.55 (m, 1H), 8.35 (s, 1H), 7.96 (m, 4H), 7.77 (d, J = 6.9Hz, 2H), 7.46-7.36 (m, 5H), 5.47 (s, 2H), 2.33 (s, 3H).

Example 5 (16)

5-phenyl-2-(2-[N-phenyl-N-methylamino] ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.41 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 10.91 (brs, 1H), 8.30 (s, 1H), 7.93 (d, J = 8.4Hz, 2H), 7.76 (d, J = 8.4Hz, 2H), 7.40 (m, 5H), 7.16 (t, J = 8.4Hz, 2H), 6.77 (d, J = 8.4Hz, 2H), 6.61 (t, J = 8.4Hz, 1H), 4.50 (t, J = 6.0Hz, 2H), 3.78 (t, J = 6.0Hz, 2H), 2.97 (s, 3H), 2.34 (s, 3H).

Example 5 (17)

6-phenyl-2-(2-[N-methyl-N-phenylamino] ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

NMR ($CDCl_3$): δ 8.21 (s, 1H), 8.07 (d, J = 7.8Hz, 2H), 7.75 (d, J = 7.8Hz, 2H), 7.48-7.29 (m, 11H), 4.49 (br, 2H), 4.00 (br, 2H), 3.31 (br, 3H), 2.41 (s, 3H).

Reference Example 3

2-bromo-6-methyl-3-(4-methylphenyl sulfonyl amino) pyrazine

Instead of 2,6-dibromo-3-aminopyrazine, using 2-bromo-3-amino-6-methylpyrazine, operation same as in Reference Example 1 was made and the title compound having the following physical property values was obtained.

TLC : Rf 0.61 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 10.82 (br, 1H), 8.13 (s, 1H), 7.85 (d, J = 8.1Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H).

Reference Example 4

2-bromo-6-methyl-3-(N-(4-methylphenyl sulfonyl)-N-(2-trimethylsilyl ethyl) amino) pyrazine

Polymer support triphenyl phosphine 1.73mol/g (2.53 g, catalog number: 800380, Argo Note Technology Co, Ltd.) and diethylazo dicarboxylate (1.99mL, 40 % toluene solution) were added at 0°C to compound (1 g) produced in Reference Example 3 and methylene chloride (25mL) solution of 2-(trimethylsilyl) ethanol (0.628mL). The reaction mixture was stirred for two hours at 0°C and overnight at room temperature. The reaction mixture was filtered, and it was concentrated. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 4 : 1 to 3 : 1) and the title compound having the following physical property values (320 mg) was obtained.

TLC : Rf 0.58 (hexane : ethyl acetate = 2 : 1)

NMR ($CDCl_3$): δ 7.92 (d, J = 8.4Hz, 2H), 7.30 (d, J = 8.4Hz, 2H), 7.15 (s, 1H), 3.69 (m, 2H), 2.43 (s, 3H), 2.34 (s, 3H), 0.67 (m, 2H), -0.07 (s, 9H).

Reference Example 5

6-methyl-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(N-(4-methylphenyl sulfonyl)-N-(2-trimethylsilyl ethyl) amino) pyrazine

Instead of benzyl alcohol and the compound produced in Reference Example 4, using 3,4-dimethoxybenzyl alcohol, the same procedures as in Example 1 was made and the title compound having the following physical property values was obtained.

TLC = Rf 0.56 (hexane : ethyl acetate = 1 : 1).

Example 6

6-methyl-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine
Compound produced in Reference Example 5 was dissolved in excess IN fluorinated tetrabutyl ammonium. The mixture was stirred at room temperature for one hour, and it was concentrated. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 3 : 1 to 2 : 1) and the compound of this invention having the following physical property values (88 mg) was obtained.
TLC : Rf 0.45 (hexane : ethyl acetate = 1 : 1)
NMR (d6-DMSO): δ 10.58 (br, 1H), 7.82 (d, J=8.1Hz, 2H), 7.61 (s, 1H), 7.32 (d, J = 8.1Hz, 2H), 7.13 (d, J = 1.5Hz, 1H), 7.03 (dd, J = 8.1, 1.5Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.27 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H).

Example 6 (1)

6-methyl-2-((3-(2-dimethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine
Using 3-(2-dimethylaminoethyl) oxy-4-methoxybenzyl alcohol instead of 3,4-dimethoxybenzyl alcohol, operation same as in Reference Example 5 to Example 6 was made, and the compound of this invention having the following physical property values was obtained.
TLC : Rf 0.36 (chloroform : methanol = 10 : 1)
NMR (d6-DMSO): δ 7.78 (d, J = 8.1Hz, 2H), 7.52 (s, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 1.8Hz, 1H), 7.04 (dd, J = 8.1, 1.8 Hz, 1H), 6.95 (d, J = 8.1Hz, 1H), 5.23 (s, 2H), 4.06 (t, J= 5.1Hz, 2H), 3.75 (s, 3H), 2.76 (t, J = 5.1 Hz, 2H), 2.33 (s, 3H), 2.32 (s, 6H), 2.23 (s, 3H).

Reference Example 6

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-aminopyrazine
Using 3,4-dimethoxybenzyl alcohol instead of 2,6-dibromo-3-aminopyrazine and benzyl alcohol, the same procedures as in Example 1 was made, and the title compound having the following physical property values was obtained.
TLC : Rf 0.35 (hexane : ethyl acetate = 1 : 1)
NMR (d6-DMSO): δ 7.60 (s, 1H), 7.13 (d, J = 1.8Hz, 1H), 7.02 (dd, J = 8.4, 1.8Hz, 1H), 6.93 (d, J = 8.4Hz, 1H), 6.49 (br, 2H), 3.76 (s, 3H), 3.74 (s, 3H).

Example 7

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine
Using 4-chlorobenzene sulphonyl chloride instead of the compound produced in Reference

Example 6 and 4-methylbenzene sulphonyl chloride, operation same as in Reference Example 1 was made, and the compound of this invention having the following physical property values was obtained.

TLC : Rf 0.50 (benzene : ethyl acetate = 3 : 1)

NMR (d6-DMSO): δ 11.25 (br, 1H), 7.92 (m, 3H), 7.63 (d, J = 9.0Hz, 2H), 7.14 (d, J = 1.8Hz, 1H), 7.04 (dd, J = 8.1, 1.8Hz, 1H), 6.95 (d, J = 8.1Hz, 1H), 5.28 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3).

Examples 7(1)-7 (4)

The compound produced in Reference Example 6 and 4-chlorobenzene sulphonyl chloride were replaced by corresponding sulphonyl chloride derivative and the same operation as in Example 7 was carried out, and the compounds of this invention shown below were obtained.

Example 7 (1)

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(phenylsulfonyl amino) pyrazine.

TLC : Rf 0.52 (benzene : ethyl acetate = 3 : 1)

NMR (d6-DMSO): δ 11.15 (br, 1H), 7.97-7.91 (m, 3H), 7.64-7.53 (m, 3H), 7.15 (d, J = 2.1Hz, 1H), 7.05 (dd, J = 8.4, 2.1Hz, 1H), 6.95 (d, J = 8.4Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H).

Example 7 (2)

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

TLC : Rf 0.48 (benzene : ethyl acetate = 3 : 1)

NMR (d6-DMSO): δ 11.18 (br, 1H), 8.01 (m, 2H), 7.92 (s, 1H), 7.40 (t, J = 8.7Hz, 2H), 7.14 (d, J = 2.4Hz, 1H), 7. 05 (dd, J = 8.1, 2.4Hz, 1H), 6.96 (d, J = 8.4Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H).

Example 7 (3)

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(2-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.60 (benzene : ethyl acetate = 3 : 1)

NMR (d6-DMSO): δ 11.10 (br, 1H), 7.93 (s, 1H), 7.75 (m, 2H), 7.44 (d, J = 5.1Hz, 2H), 7.15 (d, J = 1.8Hz, 1H), 7.05 (dd, J = 8.4, 1.8Hz, 1H), 6.95 (d, J = 8.4Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.36 (s, 3H).

Example 7 (4)

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(3-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.60 (benzene : ethyl acetate = 3 : 1)

NMR (d6-DMSO): δ 11.32 (br, 1H), 7.92 (m, 1H), 7.83 (s, 1H), 7.50 (dt, J = 1.2, 7.5Hz, 1H), 7.35 (m, 2H), 7.15 (d, J = 1.2Hz, 1H), 7.03 (dd, J = 8.1, 1.8Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 5.30 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.57 (s, 3H).

Example 8

6-(4-methylphenyl)-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

Dichlorobis (triphenyl phosphine) palladium (II) (4.9 mg, 5%N-methylpyrrolidone solution) was added to a solution in water (0.5mL) and 1,2-dimethoxyethane (1 mL) of the compound produced in Example 1 (2) (70 mg), 4-methylphenyl boric acid (38 mg) and sodium carbonate (60 mg). The reaction mixture was stirred at 80°C for two hours. 2N hydrochloric acid was added to the reaction mixture, and extraction was carried out with chloroform. The extract was washed with saturated sodium chloride aqueous solution and dried with anhydrous magnesium sulphate, and concentration was carried out. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 5 : 1 to 3 : 1) and the compound of this invention having the following physical property values (48 mg) was obtained.

TLC : Rf 0.46 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 10.88 (br, 1H), 8.31 (s, 1H), 7.90 (d, J = 8.4Hz, 2H), 7.88 (d, J = 8.4Hz, 2H), 7.36 (d, J = 8.1Hz, 2H), 7.26 (d, J = 8.1Hz, 2H), 7.20 (d, J = 1.8Hz, 1H), 7.08 (dd, J = 8.1, 1.8Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.43 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H).

Examples 8(1)-8(3)

Instead of 4-methylphenyl boric acid, using the corresponding boric acid derivative, operation same as in Example 8 was made, and the compounds of this invention shown below were obtained.

Example 8 (1)

6-(3-aminophenyl)-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.31 (hexane : ethyl acetate = 1 : 2)

NMR (d6-DMSO): δ 8.17 (s, 1H), 7.87 (d, J = 8.1Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 9.3Hz, 2H), 7.10 (m, 3H), 6.94 (d, J = 8.1Hz, 1H), 6.58 (dt, J=7.5, 2.1Hz, 1H), 5.42 (s, 2H), 3.73 (s, 6H), 2.35 (s, 3H).

Example 8 (2)

6-(3-formylphenyl)-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

TLC: Rf 0.36 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 11.04 (br, 1H), 10.07 (s, 1H), 8.53 (s, 1H), 8.44 (s, 1H), 8.33 (d, J = 7.8Hz, 1H), 7.90 (m, 3H), 7.68 (t, J = 7.8Hz, 1H), 7.36 (d, J = 7.8Hz, 2H), 7.20 (d, J = 1-8Hz, 1H), 7.12 (dd, J = 8.1, 1.8Hz, 1H), 6.94 (d, J = 8.4Hz, 1H), 5.46 (s, 2H), 3.72 (s, 6H), 2.35 (s, 3H).

Example 8 (3)

6-(3-methoxyphenyl)-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

TLC : Rf 0.40 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 10.95 (br, 1H), 8.35 (s, 1H), 7.84 (d, J = 8.1Hz, 2H), 7.57 (d, J = 8.1Hz, 1H), 7.51 (m, 1H), 7.35 (m, 3H), 7.19 (d, J = 1.8Hz, 1H), 7.08 (dd, J = 7.8, 1.8 Hz, 1H), 6.94 (m, 2H), 5.43 (s, 2H), 3.79 (s, 3H), 3.72 (s, 6H), 2.34 (s, 3H).

Example 9

2-((3-dimethylaminophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

To methylene chloride (8mL) solution of compound (367 mg) produced in Example 3 (5) was added 37 % formaldehyde aqueous solution (297 μl) at room temperature. Triacetoxy sodium borohydride (839 mg) was added at 0°C to the mixture. The reaction mixture was stirred at room temperature for four hours. Water was added to the reaction mixture, and extraction was carried out with ethyl acetate. The extract was dried with anhydrous magnesium sulphate, and concentration was carried out. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and the compound of this invention having the following physical property values (328 mg) was obtained.

TLC : Rf 0. 65 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 10.90 (s, 1H), 7.88 (d, J = 8.1Hz, 2H), 7.78-7.66 (m, 2H), 7.36 (d, J = 8.1Hz, 2H), 7.17 (t, J = 8.4Hz, 1H), 6.84 (brs, 1H), 6.77 (brd, J = 7.8 Hz, 1H), 6.68 (m, 1H), 5.33 (s, 2H), 2.89 (s, 6H), 2.36 (s, 3H).

Example 9 (1)

6-(3-dimethylaminophenyl)-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

Instead of compound produced in Example 3 (5), operation same as in Example 9 was carried out using compound produced in Example 8 (1), and the compound of this invention having the

following physical property values was obtained.

TLC : Rf 0.47 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 10.90 (br, 1H), 8.30 (s, 1H), 7.88 (d, J = 8.4Hz, 2H), 7.36 (d, J = 8.4Hz, 2H), 7.28-7.18 (m, 4H), 7.07 (dd, J = 8.1, 1.2Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.74 (m, 1H), 5.44 (s, 2H), 3.72 (s, 6H), 2.93 (s, 6H), 2.35 (s, 3H).

Example 10

2-((3-acetylaminophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

To methylene chloride (6mL) solution of compound (150 mg) produced in Example 3 (5) were added pyridine (131 μl) and acetic anhydride (76 μl). The reaction mixture was stirred at room temperature for two hours. Ethyl acetate was added to the reaction mixture and was washed with 2N hydrochloric acid and was dried with anhydrous magnesium sulphate, and concentration was carried out. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 1 : 2) and the compound of this invention having the following physical property values (153 mg) was obtained.

TLC : Rf 0.22 (hexane : ethyl acetate = 1 : 2)

NMR (d6-DMSO): δ 10.92 (s, 1H), 9.98 (s, 1H), 7.88 (d, J = 8.4Hz, 2H), 7.80-7.68 (m, 2H), 7.63 (s, 1H), 7.56 (d, J = 7.5Hz, 1H), 7.36 (d, J = 8.4Hz, 2H), 7.30 (t, J = 7.5Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 5.37 (s, 2H), 2.36 (s, 3H), 2.04 (s, 3H).

Example 11

6-bromo-2-((3-(2-dimethylaminoethyl oxy)-4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine • sodium salt

1N sodium hydroxide aqueous solution (0.217mL) was added to ethanol (2mL) solution of compound produced in Example 1 (3) (120 mg). The reaction mixture was stirred at 80°C for one hour. The reaction mixture was concentrated, and the compound of this invention having the following physical property values (94 mg) was obtained.

TLC : Rf 0.32 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 7.62 (d, J = 8.4Hz, 2H), 7.33 (s, 1H), 7.10 (m, 3H), 7.00 (dd, J = 8.4, 1.8Hz, 1H), 6.93 (d, J = 8.4Hz, 1H), 5.08 (s, 2H), 4.02 (t, J = 6.0Hz, 2H), 3.74 (s, 3H), 2.61 (t, J = 6.0Hz, 2H), 2.27 (s, 3H), 2.20 (s, 6H).

Example 12

6-bromo-2-((pyridine-1-oxide-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine

To chloroform (5mL) solution of compound produced with Example 1 (1) (500 mg) was added 70% m-chloroperbenzoic acid (340 mg) at 0°C. The reaction mixture was stirred at room

temperature for two hours. The reaction mixture was diluted with ethyl acetate and was washed with saturated sodium chloride aqueous solution and was dried with anhydrous magnesium sulphate, and concentration was carried out. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 1 : 1 to 1 : 2 to 0 : 1 to ethyl acetate : methanol = 5 : 1 to 3 : 1) and the compound of this invention having the following physical property values (317 mg) was obtained.

TLC: Rf 0.54 (chloroform : methanol = 10 : 1)

NMR (d6-DMSO): δ 11.28 (br, 1H), 8.58 (s, 1H), 8.19 (m, 1H), 7.89 (s, 1H), 7.83 (d, J = 8.1Hz, 2H), 7.46 (m, 2H), 7.34 (d, J = 8.1Hz, 2H), 5.32 (s, 2H), 2.35 (s, 3H).

Example 13

6-bromo-2-((1-methylpyridinium-3-yl) methyloxy)-3-(4-methylphenyl sulfonyl amino) pyrazine • chloride

To acetone (5mL) solution of compound produced in Example 1 (1) (300 mg) was added methyl iodide (64 μL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated. The obtained residue methanol solution was purified by passing through chloride exchange resin (pre-washing: methanol x 2, water x 2, methanol x 2), and the compounds of this invention having the following physical property values (288 mg) was obtained.

NMR (d6-DMSO): δ 11.30 (br, 1H), 9.38 (s, 1H), 9.02 (d, J = 6.0Hz, 1H), 8.75 (d, J = 6.0Hz, 1H), 8.20 (dd, J = 8.1, 6.0Hz, 1H), 8.00 (s, 1H), 7.89 (d, J = 8.1Hz, 2H), 7.36 (d, J = 8.1Hz, 2H), 5.58 (s, 2H), 4.41 (s, 3H), 2.35 (s, 3H).

Reference Example 7

2-chloro-3-(3-methylphenyl sulfonyl amino) quinoxaline

The same operation as in Reference Example 2 was carried out using 2,3-dichloroquinoxaline instead of 2,3-dichloro pyrazine, and 3-methylbenzene sulfonamide instead of 4-methylbenzene sulfonamide and the title compound having the following physical property values was obtained.

TLC : Rf 0.40 (hexane : ethyl acetate = 1 : 1)

NMR (d6-DMSO): δ 8.12 (m, 2H), 7.87 (m, 2H), 7.71 (t, J = 7.8Hz, 1H), 7.61 (t, J = 7.8Hz, 1H), 7.42 (m, 2H), 2.45 (s, 3H).

Reference Example 8

(Hereinafter Pol in the formula denotes 1 % divinylbenzene copolymer type polystyrene resin)

Wang resin (Watanabe Chemical Industry Co, Ltd, 1 % divinylbenzene copolymer type polystyrene, 100-200 mesh, catalog number A00110, 0.82 mmol/g, 4.0 g) was suspended in anhydrous tetrahydrofuran (40 mL) and compound (1.82 g) produced in Reference Example 7, triphenyl phosphine (1.29 g) and toluene solution (2.24mL) of 40 % diethyl azodicarboxylate ester were added successively under argon atmosphere at -78°C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered. The obtained resin was washed successively with tetrahydrofuran (40mL) three times, with methanol (40mL) twice and with methylene chloride (40mL) four times, and it was dried, and compound (1) (5.36 g) was obtained.

Reference Example 9

The compound (1) (750 mg) produced in Reference Example 8 was suspended in anhydrous tetrahydrofuran (6 mL), and thereto were added 2-phenoxy ethanol (1.15 mL) and tetrahydrofuran solution (2.3 mL) of 1.0M fluorinated tetrabutyl ammonium successively. The reaction mixture was stirred at 60°C for 24 hours. The reaction mixture was cooled to room temperature and was filtered. The obtained resin was washed successively with tetrahydrofuran (10mL) three times and with methylene chloride (10mL) three times, and it was dried, and compound (2) (834 mg) was obtained.

Example 14

2-(2-phenoxy ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline

Compound (2) (834 mg) produced in Reference Example 9 was suspended at room temperature in 1,2-dichloromethane solution (10mL) of 50 % trifluoroacetic acid. The reaction mixture was stirred at room temperature for two hours. The reaction mixture was filtered, and obtained resin was washed three times with 1,2-dichloromethane solution (10mL) of 50 % trifluoroacetic acid. The obtained filtrate and washing liquid were recovered, and it was concentrated, and the compound of this invention having the following physical property values (168 mg) was obtained

TLC : Rf 0.56 (hexane : ethyl acetate = 3 : 2)

NMR (d6-DMSO): δ 11.34 (br, 1H), 8.10-7.85 (m, 2H), 7.84-7.62 (m, 2H), 7.60-7.40 (m, 4H), 7.32 (t, J = 8.1Hz, 2H), 7.02 (d, J = 8.1Hz, 2H), 6.97 (t, J = 8.1Hz, 1H), 4.77 (m, 2H), 4.45 (m, 2H), 2.41 (s, 3H);

HPLC retention time [minute]: 4.18,

Mass data : 893 $(2M+Na)^+$, 436 $(M+H)^+$.

Examples 14 (1)-14 (210)

Using 2,3-dichloroquinoxaline, the corresponding sulfonamide derivative and the corresponding alcohol derivative, the same operations as in Reference Example 7 to Reference Example 8 to Reference Example 9 to Example 14 were carried out, and the compounds of this invention shown below were obtained.

Example 14 (1)

2-((pyridine-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.34,

Mass data : 813 $(2M+H)^+$, 407 $(M+H)^+$.

Example 14 (2)

2-((pyridine-4-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.37,

Mass data : 835 $(2M+Na)^+$, 407 $(M+H)^+$.

Example 14 (3)

2-(2-[pyridine-2-yl] ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 863 $(2M+Na)^+$, 421$(M+H)^+$.

Example 14 (4)

2-(3-[pyridine-3-yl] propyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.HPLC retention time (minutes) : 3.36,

Mass data : 923 $(2M+Na)^+$, 451$(M+H)^+$.

Example 14 (5)

2-(2-(N-methyl-N-benzylamino) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.50,

Mass data : 463 $(M+H)^+$, 242.

Example 14 (6)

2-(2-[N-methyl-N-phenylamino] ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.64,

Mass data : 449 $(M+H)^+$.

Example 14 (7)

2-(2-(3,5-dimethylpyrazol-1-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 3.61,
Mass data : 438 $(M+H)^+$.

Example 14 (8)

2-(2-phenoxy ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 4.15,
Mass data : 893 $(2M+Na)^+$, 436 $(M+H)^+$

Example 14 (9)

2-(3-phenylpropyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline
HPLC retention time (minutes) : 4.31,
Mass data : 889 $(2M+Na)^+$, 434 $(M+H)^+$.

Example 14 (10)

2-(4-phenylbutyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 4.40,
Mass data : 917 $(2M+Na)^+$, 448$(M+H)^+$.

Example 14 (11)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 4.17,
Mass data : 873 $(2M+Na)^+$, 426 $(M+H)^+$.

Example 14 (12)

2-(3-[pyridine-3-yl] propyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 3.40,
Mass data : 435 $(M+H)^+$.

Example 14 (13)

2-(3-benzyloxy propyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 4.23,
Mass data : 464 $(M+H)^+$.

Example 14 (14)

2-(2-(pyridine-2-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.34,

Mass data : 421 $(M+H)^+$.

Example 14 (15)

2-(3-(pyridine-2-yl) propyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 435 $(M+H)^+$.

Example 14 (16)

2-(2-(pyridine-4-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.36,

Mass data : 421 $(M+H)^+$.

Example 14 (17)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.93,

Mass data : 821 $(2M+Na)^+$, 400 $(M+H)^+$.

Example 14 (18)

2-(cyclohexylmethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.47,

Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$.

Example 14 (19)

2-(2-[piperidine-1-yl] ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.37,

Mass data : 427 $(M+H)^+$.

Example 14 (20)

2-(2-cyclopentyl ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.48,

Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$.

Example 14 (21)

2-(2-[morpholine-4-yl] ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.30,

Mass data : 429 $(M+H)^+$.

Example 14 (22)

2-(2-(pyrazol-1-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.75,

Mass data : 410 $(M+H)^+$

Example 14 (23)

2-(2-cyclopropylethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.20,

Mass data : 789 $(2M+Na)^+$, 384 $(M+H)^+$.

Example 14 (24)

2-((pyridine-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 407 $(M+H)^+$, 242.

Example 14 (25)

2-(2-cyclohexyl ethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.55,

Mass data : 873 $(2M+Na)^+$, 426 $(M+H)^+$.

Example 14 (26)

2-(3-(piperidine-1-yl) propyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.42,

Mass data : 441 $(M+H)^+$.

Example 14 (27)

2-[cyclopentylmethyl oxy]-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.35,

Mass data : 817 $(2M+Na)^+$, 398 $(M+H)^+$.

Example 14 (28)

2-(2-phenylethyl oxy)-3-(4-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.21,

Mass data : 420 $(M+H)^+$.

Example 14 (29)

2-((pyridine-2-yl) methyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 393 $(M+H)^+$, 302.

Example 14 (30)

2-((pyridine-2-yl) methyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.38,

Mass data : 407 $(M+H)^+$, 316.

Example 14 (31)

2-((pyridine-2-yl) methyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.42,

Mass data : 407 $(M+H)^+$.

Example 14 (32)

2-((pyridine-2-yl) methyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.36,

Mass data : 423 $(M+H)^+$.

Example 14 (33)

2-(2-cyclohexyl ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.48,

Mass data : 412 $(M+H)^+$.

Example 14 (34)

2-(2-cyclohexyl ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.57,

Mass data : 426 $(M+H)^+$.

Example 14 (35)

2-(2-cyclohexyl ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.59,

Mass data : 426 $(M+H)^+$.

Example 14 (36)

2-(2-cyclohexyl ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.50,

Mass data : 442 $(M+H)^+$.

Example 14 (37)

2-(3-(piperidine-1-yl) propyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 427 $(M+H)^+$.

Example 14 (38)

2-(3-[piperidine-1-yl] propyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 441 $(M+H)^+$.

Example 14 (39)

2-(3-[piperidine-1-yl] propyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLX retention time (minutes) : 3.42,

Mass data : 441 $(M+H)^+$.

Example 14 (40)

2-(3-(piperidine-1-yl) propyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.36, Mass data. 457 $(M+H)^+$.

Example 14 (41)

2-(cyclopentylmethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.26,

Mass data : 789 $(2M+Na)^+$, 384 $(M+H)^+$.

Example 14 (42)

2-[cyclopentylmethyl oxy]-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.35,

Mass data : 817 $(2M+Na)^+$, 398 $(M+H)^+$.

Example 14 (43)

2-(cyclopentylmethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.35,

Mass data : 817 $(2M+Na)^+$, 398 $(M+H)^+$

Example 14 (44)

2-[cyclopentylmethyl oxy]-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.28,

Mass data : 849 $(2M+Na)^+$, 414 $(M+H)^+$.

Example 14 (45)

2-(2-phenylethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.13,

Mass data : 833 $(2M+Na)^+$, 406 $(M+H)^+$.

Example 14 (46)

2-(2-phenylethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.22,

Mass data : 861 $(2M+Na)^+$, 420 $(M+H)^+$

Example 14 (47)

2-(2-phenylethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.23,

Mass data : 861 $(2M+Na)^+$, 420 $(M+H)^+$.

Example 14 (48)

2-(2-phenylethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.15,

Mass data : 893 $(2M+Na)^+$, 436 $(M+H)^+$.

Example 14 (49)

2-(2-(N-methyl-N-benzylamino) ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.49,

Mass data : 463 $(M+H)^+$.

Example 14 (50)

2-(2-(N-methyl-N-benzylamino) ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.49,

Mass data : 463 $(M+H)^+$.

Example 14 (51)

2-(2-[N-methyl-N-benzylamino] ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 449 $(M+H)^+$.

Example 14 (52)

2-(2-[N-methyl-N-benzylamino] ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.42,

Mass data : 479 $(M+H)^+$.

Example 14 (53)

2-(2-[N-methyl-N-phenylamino] ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.67,

Mass data : 449 $(M+H)^+$.

Example 14 (54)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.67, Mass data. 449 $(M+H)^+$

Example 14 (55)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.58,

Mass data : 435 $(M+H)^+$.

Example 14 (56)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.62,

Mass data : 465 $(M+H)^+$.

Example 14 (57)

2-(2-[3,5-dimethylpyrazol-1-yl] ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.60,

Mass data : 897 $(2M+Na)^+$, 438 $(M+H)^+$.

Example 14 (58)

2-(2-(3,5-dimethylpyrazol-1-yl) ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.64,

Mass data : 897 $(2M+Na)^+$, 438 $(M+H)^+$.

Example 14 (59)

2-(2-(3,5-dimethylpyrazol-1-yl) ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.51,

Mass data : 869 $(2M+Na)^+$, 424 $(M+H)^+$.

Example 14 (60)

2-(2-(3,5-dimethylpyrazol-1-yl) ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.55,

Mass data : 929 $(2M+Na)^+$, 454 $(M+H)^+$.

Example 14 (61)

2-(2-phenoxy ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.15,

Mass data : 893 $(2M+Na)^+$, 436 $(M+H)^+$

Example 14 (62)

2-(3-benzyloxy propyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.22,

Mass data : 949 $(2M+Na)^+$, 464 $(M+H)^+$

Example 14 (63)

2-(2-phenoxy ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.06,

Mass data : 865 $(2M+Na)^+$, 422 $(M+H)^+$.

Example 14 (64)

2-(2-phenoxy ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.08,

Mass data : 925 $(2M+Na)^+$, 452 $(M+H)^+$.

Example 14 (65)

2-(3-phenylpropyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.32,

Mass data : 889 $(2M+Na)^+$, 434 $(M+H)^+$, 120.

Example 14 (66)

2-(3-phenylpropyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.32,

Mass data : 889 $(2M+Na)^+$, 434 $(M+H)^+$, 120.

Example 14 (67)

2-(3-phenylpropyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.22,

Mass data : 861 $(2M+Na)^+$, 420 $(M+H)^+$, 120.

Example 14 (68)

2-(3-phenylpropyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.24,

Mass data : 921 $(2M+Na)^+$, 450 $(M+H)^+$, 120.

Example 14 (69)

2-(4-phenylbutyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.39,

Mass data : 917 $(2M+Na)^+$, 448 $(M+H)^+$.

Example 14 (70)

2-(4-phenylbutyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.41,

Mass data : 917 $(2M+Na)^+$, 448 $(M+H)^+$.

Example 14 (71)

2-(4-phenylbutyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.32,

Mass data : 889 $(2M+Na)^+$, 434 $(M+H)^+$.

Example 14 (72)

2-(4-phenylbutyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.32,

Mass data : 949 $(2M+Na)^+$, 464 $(M+H)^+$.

Example 14 (73)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.17, Mass data, 873 $(2M+Na)^+$, 426 $(M+H)^+$.

Example 14 (74)

2-(2-[thiophen-2-yl] ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline

HPLC retention time (minutes) : 4.17,

Mass data : 873 $(2M+Na)^+$, 426 $(M+H)^+$.

Example 14 (75)

2-(2-[thiophen-2-yl] ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.09,

Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$.

Example 14 (76)

2-(2-[thiophen-2-yl] ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HFLC retention time (minutes) : 4.10,

Mass data : 905 $(2M+Na)^+$, 442 $(M+H)^+$.

Example 14 (77)

2-(3-(pyridine-3-yl) propyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.38,

Mass data : 891 $(2M+Na)^+$, 435 $(M+H)^+$.

Example 14 (78)

2-(3-(pyridine-3-yl) propyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 891 $(2M+Na)^+$, 435 $(M+H)^+$.

Example 14 (79)

2-(3-(pyridine-3-yl) propyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 863 $(2M+Na)^+$, 421$(M+H)^+$.

Example 14 (80)

2-(3-benzyloxy propyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.22,

Mass data : 949 $(2M+Na)^+$, 464 $(M+H)^+$.

Example 14 (81)

2-(3-benzyloxy propyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.13,

Mass data : 921 $(2M+Na)^+$, 450 $(M+H)^+$.

Example 14 (82)

2-(3-(benzyloxy) propyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.13,

Mass data : 981 $(2M+Na)^+$, 480 $(M+H)^+$.

Example 14 (83)

2-(2-[pyridine-2-yl] ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.34,

Mass data : 863 $(2M+Na)^+$, 421 $(M+H)^+$.

Example 14 (84)

2-(2-(pyridine-2-yl) ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.27,

Mass data : 835 $(2M+Na)^+$, 407 $(M+H)^+$.

Example 14 (85)

2-(2-(pyridine-2-yl) ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.31,

Mass data : 895 $(2M+Na)^+$, 437 $(M+H)^+$.

Example 14 (86)

2-(3-(pyridine-2-yl) propyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.36,

Mass data : 891 $(2M+Na)^+$, 435 $(M+H)^+$.

Example 14 (87)

2-(3-[pyridine-2-yl] propyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.38,

Mass data : 891 $(2M+Na)^+$, 435 $(M+H)^+$

Example 14 (88)

2-(3-[pyridine-2-yl] propyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.31,

Mass data : 863 $(2M+Na)^+$, 421 $(M+H)^+$.

Example 14 (89)

2-(3-[pyridine-2-yl] propyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 923 $(2M+Na)^+$, 451 $(M+H)^+$, 332.

Example 14 (90)

2-(2-(pyridine-4-yl) ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 841 $(2M+H)^+$, 421 $(M+H)^+$

Example 14 (91)

2-(2-[pyridine-4-yl] ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.34,

Mass data : 841 $(2M+H)^+$, 421 $(M+H)^+$.

Example 14 (92)

2-(2-(pyridine-4-yl) ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.27,

Mass data : 813 $(2M+H)^+$, 407 $(M+H)^+$.

Example 14 (93)

2-(2-[pyridine-4-yl] ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.29,

Mass data : 873 $(2M+H)^+$, 437 $(M+H)^+$.

Example 14 (94)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 3.93,
Mass data : 821 $(2M+Na)^+$, 400 $(M+H)^+$.

Example 14 (95)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 3.93,
Mass data : 821 $(2M+Na)^+$, 400 $(M+H)^+$.

Example 14 (96)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(phenylsulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 3.82,
Mass data : 793 $(2M+Na)^+$, 386 $(M+H)^+$.

Example 14 (97)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 3.84,
Mass data : 853 $(2M+Na)^+$, 416 $(M+H)^+$.

Example 14 (98)

2-(cyclohexylmethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 4.50,
Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$.

Example 14 (99)

2-((cyclohexyl) methyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.
HPLC retention time (minutes) : 4.48,
Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$.

Example 14 (100)

2-(cyclohexylmethyl oxy)-3-(phenylsulfonyl amino) quinoxaline
HPLC retention time (minutes) : 4.37,
Mass data : 817 $(2M+Na)^+$, 398 $(M+H)^+$

Example 14 (101)

2-[cyclohexylmethyl oxy]-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.39,

Mass data : 877 $(2M+Na)^+$, 428 $(M+H)^+$.

Example 14 (102)

2-(2-[piperidine-1-yl] ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.35,

Mass data : 427 $(M+H)^+$.

Example 14 (103)

2-(2-(piperidine-1-yl) ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.36,

Mass data : 427 $(M+H)^+$.

Example 14 (104)

2-(2-(piperidine-1-yl) ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.29,

Mass data : 413 $(M+H)^+$.

Example 14 (105)

2-(2-[piperidine-1-yl] ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 443 $(M+H)^+$.

Example 14 (106)

2-(2-cyclopentyl ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.46,

Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$.

Example 14 (107)

2-(2-cyclopentyl ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.46,

Mass data : 845 (2M+Na) +, 412 $(M+H)^+$.

Example 14 (108)

2-(2-cyclopentyl ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.37,

Mass data : 817 $(2M+Na)^+$, 398 $(M+H)^+$.

Example 14 (109)

2-(2-cyclopentyl ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.39,

Mass data : 877 $(2M+Na)^+$, 428 $(M+H)^+$.

Example 14 (110)

2-(2-(morpholin-4-yl) ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.27,

Mass data : 879 $(2M+Na)^+$, 429 $(M+H)^+$.

Example 14 (111)

2-(2-[morpholine-4-yl] ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.29,

Mass data : 879 $(2M+Na)^+$, 429 $(M+H)^+$.

Example 14 (112)

2-(2-(morpholin-4-yl) ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.22,

Mass data : 415 $(M+H)^+$.

Example 14 (113)

2-(2-[morpholine-4-yl] ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.25,

Mass data : 911 $(2M+Na)^+$, 445 $(M+H)^+$

Example 14 (114)

2-(2-[pyrazol-1-yl] ethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.77,

Mass data : 841 $(2M+Na)^+$, 410 $(M+H)^+$.

Example 14 (115)

2-(2-(pyrazol-1-yl) ethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.77,

Mass data : 841 $(2M+Na)^+$, 410 $(M+H)^+$.

Example 14 (116)

2-(2-[pyrazol-1-yl] ethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.67,

Mass data : 813 $(2M+Na)^+$, 396 $(M+H)^+$.

Example 14 (117)

2-(2-(pyrazol-1-yl) ethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.71,

Mass data : 873 $(2M+Na)^+$, 426 $(M+H)^+$.

Example 14 (118)

2-(2-cyclopropylethyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.21,

Mass data : 789 $(2M+Na)^+$, 384 $(M+H)^+$.

Example 14 (119)

2-(2-cyclopropylethyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.21,

Mass data : 789 $(2M+Na)^+$, 384 $(M+H)^+$.

Example 14 (120)

2-(2-cyclopropylethyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.10,

Mass data : 761 $(2M+Na)^+$, 370 $(M+H)^+$.

Example 14 (121)

2-(2-cyclopropylethyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.11,

Mass data : 821 $(2M+Na)^+$, 400 $(M+H)^+$.

Example 14 (122)

2-((pyridine-3-yl) methyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 813 $(2M+H)^+$, 407 $(M+H)^+$.

Example 14 (123)

2-((pyridine-3-yl) methyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 813 $(2M+H)^+$, 407 $(M+H)^+$.

Example 14 (124)

2-((pyridine-3-yl) methyl oxy)-3-(phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.27, Mass data, 785 $(2M+H)^+$, 393 $(M+H)^+$.

Example 14 (125)

2-((pyridine-3-yl) methyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.29,

Mass data : 845 $(2M+H)^+$, 423 $(M+H)^+$.

Example 14 (126)

2-((pyridine-4-yl) methyl oxy)-3-(2-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.31,

Mass data : 813 $(2M+H)^+$, 407 $(M+H)^+$

Example 14 (127)

2-((pyridine-4-yl) methyl oxy)-3-(3-methylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 813 $(2M+H)^+$, 407 $(M+H)^+$

Example 14 (128)

2-((pyridine-4-yl) methyl oxy)-3-(phenylsulfonyl amino) quinoxaline

HPLC retention time (minutes) : 3.25,

Mass data : 785 $(2M+H)^+$, 393 $(M+H)^+$

Example 14 (129)

2-((pyridine-4-yl) methyl oxy)-3-(4-methoxyphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.29,

Mass data : 845 $(2M+H)^+$, 423 $(M+H)^+$.

Example 14 (130)

2-(2-(N-methyl-N-benzylamino) ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 474 $(M+H)^+$.

Example 14 (131)

2-(2-(N-methyl-N-benzylamino) ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.55 ,

Mass data : 529 $(M+H)^+$.

Example 14 (132)

2-(2-[N-methyl-N-phenylamino] ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.62,

Mass data : 460 $(M+H)^+$.

Example 14 (133)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.78,

Mass data : 513 $(M+H)^+$.

Example 14 (134)

2-(2-phenoxy ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.04,

Mass data : 469 $(M+Na)^+$, 447 $(M+H)^+$.

Example 14 (135)

2-(2-phenoxy ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline

HPLC retention time (minutes) : 4.26,

Mass data : 522 $(M+Na)^+$, 500 $(M+H)^+$.

Example 14 (136)

2-(3-phenylpropyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.21,

Mass data : 467 $(2M+Na)^+$, 445 $(M+H)^+$.

Example 14 (137)

2-(3-phenylpropyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.43,

Mass data : 520 $(2M+Na)^+$, 498 $(M+H)^+$.

Example 14 (138)

2-(4-phenylbutyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.28,

Mass data : 481 $(2M+Na)^+$, 459 $(M+H)^+$.

Example 14 (139)

2-(4-phenylbutyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline

HPLC retention time (minutes) : 4.52,

Mass data : 534 $(M+Na)^+$, 5I2 $(M+H)^+$.

Example 14 (140)

2-(3-[pyridine-3-yl] propyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 446 $(M+H)^+$.

Example 14 (141)

2-(3-(pyridine-3-yl) propyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.47,

Mass data : 499 $(M+H)^+$.

Example 14 (142)

2-(3-benzyloxy propyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.11,

Mass data : 497 $(M+Na)^+$, 475 $(M+H)^+$.

Example 14 (143)

2-(3-benzyloxy propyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.34,

Mass data : 500 $(M+Na)^+$, 528 $(M+H)^+$.

Example 14 (144)

2-(2-[pyridine-2-yl] ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.27,

Mass data : 432 $(M+H)^+$.

Example 14 (145)

2-(2-(pyridine-2-yl) ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.42,

Mass data : 485 $(M+H)^+$.

Example 14 (146)

2-(3-[pyridine-2-yl] propyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.31,

Mass data : 446 $(M+H)^+$.

Example 14 (147)

2-(3-(pyridine-2-yl) propyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.47,

Mass data : 499 $(M+H)^+$.

Example 14 (148)

2-(2-(pyridine-4-yl) ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.27,

Mass data : 432 $(M+H)^+$.

Example 14 (149)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.82,

Mass data : 433 $(M+Na)^+$, 411 $(M+H)^+$.

Example 14 (150)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.06,

Mass data : 486 $(M+Na)^+$, 464 $(M+H)^+$.

Example 14 (151)

2-[cyclohexylmethyl oxy]-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.35,

Mass data : 423 $(M+H)^+$.

Example 14 (152)

2-(cyclohexylmethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.59,

Mass data : 476 $(M+H)^+$.

Example 14 (153)

2-(2-[piperidine-1-yl] ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.29,

Mass data : 438 $(M+H)^+$.

Example 14 (154)

2-(2-[piperidine-1-yl] ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.44,

Mass data : 491 $(M+H)^+$.

Example 14 (155)

2-(2-cyclopentyl ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.33,

Mass data : 423 $(M+H)^+$.

Example 14 (156)

2-(2-cyclopentyl ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.59,

Mass data : 476 $(M+H)^+$.

Example 14 (157)

2-(2-(morpholin-4-yl) ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.22,

Mass data : 440 $(M+H)^+$.

Example 14 (158)

2-(2-[morpholine-4-yl] ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.36,

Mass data : 493 $(M+H)^+$.

Example 14 (159)

2-(2-cyclopropylethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.08,

Mass data : 395 $(M+H)^+$.

Example 14 (160)

2-(2-cyclopropylethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline

HFLX retention time (minutes) : 4.33,

Mass data : 448 $(M+H)^+$.

Example 14 (161)

2-((pyridine-2-yl) methyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.34,

Mass data : 418 $(M+H)^+$.

Example 14 (162)

2-((pyridine-2-yl) methyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.53,

Mass data : 471 $(M+H)^+$.

Example 14 (163)

2-(2-cyclohexyl ethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.45,

Mass data : 437 $(M+H)^+$.

Example 14 (164)

2-(2-cyclohexyl ethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.72,

Mass data : 490 $(M+H)^+$.

Example 14 (165)

2-(3-(piperidine-1-yl) propyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.33,

Mass data : 452 $(M+H)^+$.

Example 14 (166)

2-(3-(piperidine-1-yl) propyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.49,

Mass data : 505 $(M+H)^+$.

Example 14 (167)

2-(2-phenylethyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.10,

Mass data : 453 $(M+Na)^+$, 431 $(M+H)^+$.

Example 14 (168)

2-(2-phenylethyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.34,

Mass data : 506 $(M+Na)^+$, 484 $(M+H)^+$.

Example 14 (169)

2-((pyridine-3-yl) methyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.25,

Mass data : 418 $(M+H)^+$.

Example 14 (170)

2-((pyridine-3-yl) methyl oxy)-3-(4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 471 $(M+H)^+$.

Example 14 (171)

2-((pyridine-4-yl) methyl oxy)-3-(4-cyanophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.25,

Mass data : 418 $(M+H)^+$.

Example 14 (172)

2-((pyridine-4-yl) methyl oxy)-3 (4-bromo phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.40,

Mass data : 471 $(M+H)^+$

Example 14 (173)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.80,

Mass data : 453 $(M+H)^+$.

Example 14 (174)

2-(2-phenoxy ethyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.28, Mass data, 901 $(2M+Na)^+$, 440 $(M+H)^+$.

Example 14 (175)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) : 4.32,

Mass data : 881 $(2M+Na)^+$, 430 $(M+H)^+$.

Example 14 (176)

2-(cyclopentylmethyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.50,

Mass data : 825 $(2M+Na)^+$, 402 $(M+H)^+$

Example 14 (177)

2-(2-phenylethyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.35,

Mass data : 869 $(2M+Na)^+$, 424 $(M+H)^+$.

Example 14 (178)

2-((pyridine-3-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline

HPLC retention time (minutes) : 3.44,

Mass data : 821 $(2M+H)^+$, 411 $(M+H)^+$

Example 14 (179)

2-((pyridine-4-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.44,

Mass data : 411 $(M+H)^+$.

Example 14 (180)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.91,

Mass data : 469 $(M+H)^+$

Example 14 (181)

2-(2-phenoxy ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.41,

Mass data : 933 $(2M+Na)^+$, 456 $(M+H)^+$.

Example 14 (182)

2-((pyridine-2-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.64,

Mass data : 875 $(2M+Na)^+$, 427 $(M+H)^+$.

Example 14 (183)

2-(cyclopentylmethyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.63,

Mass data : 857 $(2M+Na)^+$, 418 $(M+H)^+$.

Example 14 (184)

2-(2-phenylethyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.48,

Mass data : 901 $(2M+Na)^+$, 440 $(M+H)^+$.

Example 14 (185)

2-((pyridine-3-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.55,

Mass data : 427 $(M+H)^+$.

Example 14 (186)

2-((pyridine-4-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.55,

Mass data : 427 $(M+H)^+$.

Example 14 (187)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.93,

Mass data : 463 $(M+H)^+$.

Example 14 (188)

2-(2-phenoxy ethyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.43,

Mass data : 921 $(2M+Na)^+$, 450 $(M+H)^+$.

Example 14 (189)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) : 4.46,

Mass data : 901 $(2M+Na)^+$, 440 $(M+H)^+$.

Example 14 (190)

2-((pyridine-2-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.66,

Mass data : 863 $(2M+Na)^+$, 421 $(M+H)^+$.

Example 14 (191)

2-(cyclopentylmethyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.65,

Mass data : 845 $(2M+Na)^+$, 412 $(M+H)^+$

Example 14 (192)

2-(2-phenylethyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.50,

Mass data : 889 $(2M+Na)^+$, 434 $(M+H)^+$

Example 14 (193)

2-((pyridine-3-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.58,

Mass data : 841 $(2M+H)^+$, 421 $(M+H)^+$.

Example 14 (194)

2-((pyridine-4-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.56,

Mass data : 841 $(2M+H)^+$, 421 $(M+H)^+$.

Example 14 (195)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.04,

Mass data : 477 $(M+H)^+$.

Example 14 (196)

2-(2-phenoxy ethyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.52,

Mass data : 949 $(2M+Na)^+$, 464 $(M+H)^+$

Example 14 (197)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-propyl phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) : 4.55,

Mass data : 929 $(2M+Na)^+$, 454 $(M+H)^+$.

Example 14 (198)

2-((pyridine-2-yl) methyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.77,

Mass data : 891 $(2M+Na)^+$, 435 $(M+H)^+$.

Example 14 (199)

2-(cyclopentylmethyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.76,

Mass data : 873 $(2M+Na)^+$, 426 $(M+H)^+$

Example 14 (200)

2-(2-phenylethyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.61,

Mass data : 917 $(2M+Na)^+$, 448 $(M+H)^+$.

Example 14 (201)

2-((pyridine-3-yl) methyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.66,

Mass data : 869 $(2M+H)^+$, 435 $(M+H)^+$.

Example 14 (202)

2-((pyridine-4-yl) methyl oxy)-3-(4-propyl phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.67,

Mass data : 869 $(2M+H)^+$, 435 $(M+H)^+$.

Example 14 (203)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.04,

Mass data : 975 $(M+Na)^+$, 477 $(M+H)^+$.

Example 14 (204)

2-(2-phenoxy ethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.48,

Mass data : 949 $(2M+H)^+$, 464 $(M+H)^+$

Example 14 (205)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) : 4.54,

Mass data : 929 $(2M+Na)^+$, 454 $(M+H)^+$.

Example 14 (206)

2-((pyridine-2-yl) methyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.75,

Mass data : 891 $(2M+Na)^+$, 435 $(M+H)^+$.

Example 14 (207)

2-(cyclopentylmethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.74,

Mass data : 874 (2M+Na) +, 426$(M+H)^+$.

Example 14 (208)

2-(2-phenylethyl oxy)-B-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 4.59,

Mass data : 9170 M+Nay, 448$(M+H)^+$.

Example 14 (209)

2-((pyridine-3-yl) methyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.66,

Mass data : 869 $(2M+H)^+$, 435$(M+H)^+$.

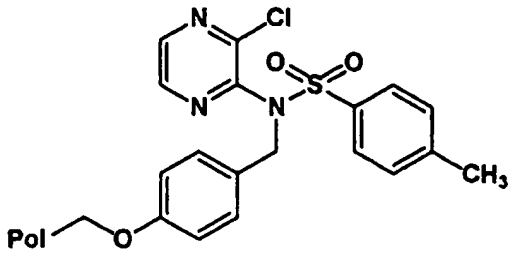
Example 14 (210)

2-((pyridine-4-yl) methyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) quinoxaline.

HPLC retention time (minutes) : 3.66,

Mass data : 891 $(2M+Na)^+$, 435$(M+H)^+$.

Reference Example 10



(3)

Using compound produced in Reference Example 2 instead of compound produced in Reference Example 7, the same operation as in Reference Example 8 was carried out, and compound (3) was obtained.

Example 15

2-(2-phenoxy ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

Compound (3) produced in Reference Example 10 (100 mg) was suspended in anhydrous 1,4-dioxane (2 mL) and, under argon atmosphere, 2-phenoxyethanol (0-214 mL), 1.6 M n-butyl lithium - hexane solution (0.267 mL) were successively added at room temperature. The reaction mixture was stirred at 100°C for 16 hours. The reaction mixture was cooled to room temperature and was filtered. The obtained resin was washed twice with tetrahydrofuran (2 mL), and it was washed four times with methanol (2 mL) and was washed five times with methylene chloride (2 mL), and thereafter, the same operation as in Example 14 was carried out, and the compounds of this invention which had the following physical property values (26 mg) were obtained.

TLC: Rf 0.89 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO)= δ 10.88 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.71 (m, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.29 (dd, J = 7.8, 7.2 Hz, 2H), 6.97 (d).

HPLC retention time (minutes) = 3.89.

Mass data = 771 $(2M+H)^+$, 386 $(M+H)^+$.

Example 15. (1)-15 (63).

Using 2,3-dichloro pyrazine, corresponding sulfonamides derivative and corresponding alcohol

derivatives, the same operation as in Reference Example 2 to Reference Example 10 to Example 15 was carried out, and the compounds of this invention shown below were obtained.

Example 15 (1)

2-(2-(N-methyl-N-benzylamino) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 413 $(M+H)^+$.

Example 15 (2)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 819 $(2M+Na)^+$, 399 $(M+H)^+$.

Example 15 (3)

2-(2-(3,5-dimethylpyrazol-1-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.29.

Mass data = 797 $(2M+Na)^+$, 388 $(M+H)^+$.

Example 15 (4)

2-(3-benzyloxy propyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.98.

Mass data = 414 $(M+H)^+$.

Example 15 (5)

2-(3-phenylpropyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.08.

Mass data = 789 $(2M+Na)^+$, 384 $(M+H)^+$.

Example 15 (6)

2-(4-phenylbutyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.16.

Mass data = 817 $(2M+Na)^+$, 398 $(M+H)^+$.

Example 15 (7)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.92.

Mass data = 773 $(2M+Na)^+$, 376 $(M+H)^+$.

Example 15 (8)

2-(3-(pyridin-3-yl) propyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.21.

Mass data = 769 $(2M+H)^+$, 385 $(M+H)^+$).

Example 15 (9)

2-(3-(pyridin-2-yl) propyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.20.

385 $(M+H)^+$ = Mass data.

Example 15 (10)

2-((tetrahydrofuran-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.60.

Mass data = 721 $(2M+Na)^+$, 350 $(M+H)^+$.

Example 15 (11)

2-(cyclohexylmethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.22.

Mass data = 745 $(2M+Na)^+$, 362 $(M+H)^+$.

Example 15 (12)

2-(2-(piperidin-1-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.19.

Mass data = 377 $(M+H)^+$.

Example 15 (13)

2-(2-cyclopentyl ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.20.

Mass data = 745 $(2M+Na)^+$, 362 $(M+H)^+$.

Example 15 (14)

2-(2-(morpholin-4-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.11.

Mass data = 379 $(M+H)^+$.

Example 15 (15)

2-(2-(pyrazol-1-yl) ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.46.

Mass data = 741 $(2M+Na)^+$, 360 $(M+H)^+$.

Example 15 (16)

2-(2-cyclopropylethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.91.

Mass data = 689 $(2M+Na)^+$, 334 $(M+H)^+$.

Example 15 (17)

2-((pyridin-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 735 $(2M+Na)^+$, 357 $(M+H)^+$.

Example 15 (18)

2-(2-cyclohexyl ethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.32.

Mass data = 773 $(2M+Na)^+$, 376 $(M+H)^+$.

Example 15 (19)

2-(3-(piperidin-1-yl) propyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.22.

Mass data = 391 $(M+H)^+$.

Example 15 (20)

2-(cyclopentylmethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.07.

Mass data = 717 $(2M+Na)^+$, 348 $(M+H)^+$.

Example 15 (21)

2-(2-phenylethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.96.

Mass data = 761 $(2M+Na)^+$, 370 $(M+H)^+$.

Example 15 (22)

2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.15.

Mass data = 713 $(2M+H)^+$, 357 $(M+H)^+$.

Example 15 (23)

2-((pyridin-4-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.14.

Mass data = 713 $(2M+H)^+$, 357 $(M+H)^+$.

Example 15 (24)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.49.

Mass data = 403 $(M+H)^+$.

Example 15 (25)

2-(2-phenoxy ethyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.99.

Mass data = 801 $(2M+Na)^+$, 390 $(M+H)^+$.

Example 15 (26)

2-(cyclopentylmethyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.17.

Mass data = 725 $(2M+ Na)^+$, 352 $(M+H)^+$, 270.

Example 15 (27)

2-(2-phenylethyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.06.

Mass data = 769 $(2M+ Na)^+$, 374 $(M+H)^+$.

Example 15 (28)

2-((pyridin-3-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.19.

Mass data = 361 $(M+H)^+$.

Example 15 (29)

2-((pyridin-4-yl) methyl oxy)-3-(4-fluorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.19.

Mass data = 361 $(M+H)^+$.

Example 15 (30)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.58.

Mass data = 419 $(M+H)^+$.

Example 15 (31)

2-(2-phenoxy ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.12.

Mass data = 406 $(M+H)^+$.

Example 15 (32)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.13.

Mass data = 396 $(M+H)^+$.

Example 15 (33)

2-(cyclopentylmethyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.30.

Mass data = 757 $(2M+ Na)^+$, 368 $(M+H)^+$.

Example 15 (34)

2-(2-phenylethyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.19.

Mass data = 801 $(2M+ Na)^+$, 390 $(M+H)^+$.

Example 15 (35)

2-((pyridin-3-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.30.

Mass data = 753 $(2M+H)^+$, 377 $(M+H)^+$).

Example 15 (36)

2-((pyridin-4-yl) methyl oxy)-3-(4-chlorophenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.30.

Mass data = 377 $(M+H)^+$.

Example 15 (37)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.64.

Mass data = 463 $(M+H)^+$.

Example 15 (38)

2-(2-phenoxy ethyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.15.

Mass data = 450 $(M+H)^+$.

Example 15 (39)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.17.

Mass data = 440 $(M+H)^+$.

Example 15 (40)

2-((pyridin-2-yl) methyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.37.

Mass data = 421 $(M+H)^+$.

Example 15 (41)

2-(cyclopentylmethyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.33.

Mass data = 845 $(2M+ Na)^+$, 412 $(M+H)^+$.

Example 15 (42)

2-(2-phenylethyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.21.

Mass data = 434 $(M+H)^+$.

Example 15 (43)

2-((pyridin-3-yl) methyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 421 $(M+H)^+$.

Example 15 (44)

2-((pyridin-4-yl) methyl oxy)-3-(4-bromo phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 421 $(M+H)^+$.

Example 15 (45)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.62.

Mass data = 413 $(M+H)^+$.

Example 15 (46)

2-(2-phenoxy ethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.15.

Mass data = 821 $(2M+ Na)^+$, 400 $(M+H)^+$.

Example 15 (47)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.15.

Mass data = 801 $(2M+ Na)^+$, 390 $(M+H)^+$.

Example 15 (48)

2-((pyridin-2-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 763 $(2M+ Na)^+$, 371 $(M+H)^+$.

Example 15 (49)

2-(cyclopentylmethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.33.

Mass data = 745 $(2M+ Na)^+$, 362 $(M+H)^+$, 280.

Example 15 (50)

2-(2-phenylethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.21.

Mass data = 789 $(2M+ Na)^+$, 384 $(M+H)^+$.

Example 15 (51)

2-((pyridin-3-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.34.

Mass data = 741 $(2M+H)^+$, 371 $(M+H)^+$.

Example 15 (52)

2-((pyridin-4-yl) methyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 763 $(2M+ Na)^+$, 371 $(M+H)^+$.

Example 15 (53)

2-(2-(N-methyl-N-phenylamino) ethyl oxy)-3-(4-propyl phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.77.

Mass data = 875 $(2M+ Na)^+$, 427 $(M+H)^+$.

Example 15 (54)

2-(2-phenoxy ethyl oxy)-3-(4-propyl phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.25.

Mass data = 849 $(2M+ Na)^+$, 414 $(M+H)^+$.

Example 15 (55)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-propyl phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.28.

Mass data = 829 $(2M+ Na)^+$, 404 $(M+H)^+$.

Example 15 (56)

2-((pyridin-2-yl) methyl oxy)-3-(4-propyl phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.49.

Mass data = 791 $(2M+ Na)^+$, 385 $(M+H)^+$.

Example 15 (57)

2-(2-phenoxy ethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.22.

Mass data = 849 $(2M+ Na)^+$, 414 $(M+H)^+$.

Example 15 (58)

2-(2-(thiophen-2-yl) ethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.26.

Mass data = 829 $(2M+ Na)^+$, 404 $(M+H)^+$.

Example 15 (59)

2-((pyridin-2-yl) methyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.49.

Mass data = 791 $(2M+ Na)^+$, 385 $(M+H)^+$.

Example 15 (60)

2-(cyclopentylmethyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.41.

Mass data = 773 $(2M+ Na)^+$, 376 $(M+H)^+$.

Example 15 (61)

2-(2-phenylethyl oxy)-3-(4-ethylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.30.

Mass data = 817 $(2M+ Na)^+$, 398 $(M+H)^+$.

Example 15 (62)

2-((pyridin-3-yl) methyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.44.

Mass data = 769 $(2M+H)^+$, 385 $(M+H)^+$.

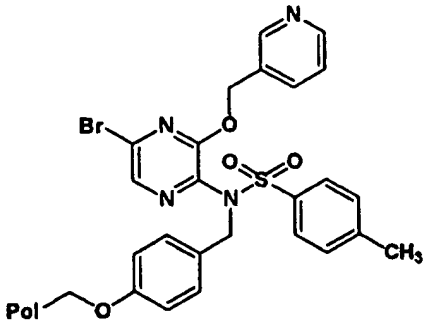
Example 15 (63)

2-((pyridin-4-yl) methyl oxy)-3-(4-(1-methylethyl) phenylsulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 791 $(2M+ Na)^+$, 385 $(M+H)^+$.

Reference Example 11



(4)

Using a compound produced in Example 1 (1) instead of compound produced in Reference Example 7, the same operation as in Reference Example 8 was carried out, and compound (4) was obtained.

Example 16

6-phenyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

Compound (4) produced in Reference Example 11 (50 mg) was suspended in 1,2-dimethoxyethane (1 mL) and, under argon atmosphere, phenyl boric acid (28 mg), 2 N sodium carbonate aqueous solution (0.30 mL), dichlorobis (triphenylphosphine) palladium (II) (4.3 mg) were successively added at room temperature. The reaction mixture was stirred at 90°C for six hours. The reaction mixture was cooled to room temperature and was filtered. The obtained resin was washed twice with 1,2-dimethoxyethane and water mixture (2 mL), it was washed twice with water (2 mL), three times with 1,2-dimethoxyethane and water mixture (2 mL), three times with 0.2 N hydrochloric acid and tetrahydrofuran liquid mixture (1 : 2) (2 mL), three times with water and tetrahydrofuran liquid mixture (1 : 2) (2 mL), three times with tetrahydrofuran (2 mL) and was washed three times with 1,2-dichloromethane (2 mL), and thereafter, the same operation as in Example 14 was carried out, and the compound of this invention (11 mg) which had the following physical property values was obtained.

TLC : Rf 0.70 (chloroform : methanol = 10 : 1).

NMR (d6-DMSO)= δ 11.05 (brs, 1H), 8.82 (d, J = 2,1 Hz, 1H), 8.54 (dd, J = 3.9, 2.1 Hz, 1H), 8.37 (s, 1H), 7.99 (dd, J = 3.9, 1.8 Hz, 3H), 7.89 (d, J = 8.1 Hz, 2H), 7.45-7.36 (m, 6H), 5.56 (s, 2H), 2.35 (s, 3H),.

HPLC retention time (minutes) = 3.49.

ESI = Mass condition (Pos. 40 V).

Mass data = 433 $(M+H)^+$.

Examples 16. (1)-16 (60).

Using corresponding boric acid derivatives instead of phenyl boric acid, the same operation as in Example 16 was carried out, and the compounds of this invention shown below were obtained.

Example 16 (1)

6-(3-nitrophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.49.

Mass data = 955 $(2M+H)^+$, 478 $(M+H)^+$.

Example 16 (2)

6-(2,4-dichlorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.71.

Mass data = 501 $(M+H)^+$.

Example 16 (3)

6-(naphthalen-1-yl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.62.

Mass data = 965 $(2M+H)^+$, 483 $(M+H)^+$.

Example 16 (4)

6-(4-fluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.53.

Mass data = 901 $(2M+H)^+$, 451 $(M+H)^+$.

Example 16 (5)

6-(4-chlorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.62.

Mass data = 933 $(2M+H)^+$, 467 $(M+H)^+$.

Example 16 (6)

6-(methylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.58.

Mass data = 893 $(2M+H)^+$, 447 $(M+H)^+$.

Example 16 (7)

6-(4-methoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.49.

Mass data = 925 $(2M+H)^+$, 463 $(M+H)^+$.

Example 16 (8)

6-(3-methylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.58.

Mass data = 893 $(2M+H)^+$, 447 $(M+H)^+$.

Example 16 (9)

6-(3-chloro-4-fluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.64.

Mass data = 969 $(2M+H)^+$, 485 $(M+H)^+$.

Example 16 (10)

6-(3,5-)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.80.

Mass data = 569 $(M+H)^+$.

Example 16 (11)

6-(3,5-dichloromethyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.75.

Mass data = 501 $(M+H)^+$.

Example 16 (12)

6-(4-phenyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.77.

Mass data = 509 $(M+H)^+$.

Example 16 (13)

6-(4-methylthio phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino)

pyrazine.

HPLC retention time (minutes) = 3.60.

Mass data = 957 $(2M+H)^+$, 479 $(M+H)^+$.

Example 16 (14)

6-(2-methylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 893 $(2M+H)^+$, 447 $(M+H)^+$.

Example 16 (15)

6-(phenanthren-9-yl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.80.

Mass data = 533 $(M+H)^+$.

Example 16 (16)

6-(3-aminophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.09.

Mass data = 895 $(2M+H)^+$, 448 $(M+H)^+$.

Example 16 (17)

6-(4-carboxy phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 953 $(2M+H)^+$, 477 $(M+H)^+$.

Example 16 (18)

6-(2-formylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 921 $(2M+H)^+$, 461 $(M+H)^+$.

Example 16 (19)

6-(3-trifluoromethylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.66.

Mass data = 501 $(M+H)^+$.

Example 16 (20)

6-(4-trifluoromethylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.67.

Mass data = 501 $(M+H)^+$.

Example 16 (21)

6-(3-formylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.40.

Mass data = 921 $(2M+H)^+$, 461 $(M+H)^+$.

Example 16 (22)

6-(3-methoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 925 $(2M+H)^+$, 463 $(M+H)^+$.

Example 16 (23)

6-(3-nitro-4-methylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.56.

Mass data = 983 $(2M+H)^+$, 492 $(M+H)^+$.

Example 16 (24)

6-(3-acetylaminophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.31.

Mass data = 979 $(2M+H)^+$, 490 $(M+H)^+$.

Example 16 (25)

6-(3-fluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.53.

Mass data = 901 $(2M+H)^+$, 451 $(M+H)^+$.

Example 16 (26)

6-(2-methoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.51.

Mass data = 925 $(2M+H)^+$, 463 $(M+H)^+$.

Example 16 (27)

6-(naphthalen-2-yl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.66.

Mass data = 965 $(2M+H)^+$, 483 $(M+H)^+$.

Example 16 (28)

6-(2-trifluoromethylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.58.

Mass data = 501 $(M+H)^+$.

Example 16 (29)

6-(3-ethoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.60.

Mass data = 953 $(2M+H)^+$, 477 $(M+H)^+$.

Example 16 (30)

6-(2-chlorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.56.

Mass data = 933 $(2M+H)^+$, 467 $(M+H)^+$.

Example 16 (31)

6-(2-fluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.51.

Mass data = 901 $(2M+H)^+$, 451 $(M+H)^+$.

Example 16 (32)

6-(4-ethylphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.67.

Mass data = 921 $(2M+H)^+$, 461 $(M+H)^+$.

Example 16 (33)

6-(3,4-dimethyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.66.

Mass data = 921 $(2M+H)^+$, 461 $(M+H)^+$.

Example 16 (34)

6-(1,3-dioxan indan-5-yl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.49.

Mass data = 953 $(2M+H)^+$, 477 $(M+H)^+$.

Example 16 (35)

6-(4-(1,1-dimethylethyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.82.

Mass data = 977 $(2M+H)^+$, 489 $(M+H)^+$.

Example 16 (36)

6-(3,4-dimethoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 985 $(2M+H)^+$, 493 $(M+H)^+$.

Example 16 (37)

6-(2,4-dimethoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.53.

Mass data = 985 $(2M+H)^+$, 493 $(M+H)^+$.

Example 16 (38)

6-(4-(1-methylethyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.75.

Mass data = 949 $(2M+H)^+$, 475 $(M+H)^+$.

Example 16 (39)

6-(4-hydroxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.31.

897 = Mass data $(2M+H)^+$, 449 $(M+H)^+$.

Example 16 (40)

6-(3-(1-methylethyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.73.

Mass data = 949 $(2M+H)^+$, 475 $(M+H)^+$.

Example 16 (41)

6-(4-methyl carbonyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 949 $(2M+H)^+$, 475 $(M+H)^+$.

Example 16 (42)

6-(3-methyl carbonyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.44.

Mass data = 949 $(2M+H)^+$, 475 $(M+H)^+$.

Example 16 (43)

6-(3,4,5-trimethoxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.45.

Mass data = 523 $(M+H)^+$.

Example 16 (44)

6-(2,3-dichlorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.66.

Mass data = 501 $(M+H)^+$.

Example 16 (45)

6-(4-(2-carboxy ethenyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.36.

Mass data = 503 $(M+H)^+$.

Example 16 (46)

6-(4-benzyloxyphenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.78.

Mass data = 539 $(M+H)^+$.

Example 16 (47)

6-(4-phenyl-3-fluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.80.

Mass data = 527 $(M+H)^+$.

Example 16 (48)

6-(3-(2-carboxy ethenyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.40.

Mass data = 503 $(M+H)^+$.

Example 16 (49)

6-(4-(2-nitroethenyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.40.

Mass data = 504 $(M+H)^+$.

Example 16 (50)

6-(3-phenyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.77.

Mass data = 509 $(M+H)^+$.

Example 16 (51)

6-(4-(2-carboxyethyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 505 $(M+H)^+$.

Example 16 (52)

6-(3,5-difluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.18.

Mass data = 937 $(2M+H)^+$, 469 $(M+H)^+$.

Example 16 (53)

6-(4-ethylthio phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.67.

Mass data = 985 $(2M+H)^+$, 493 $(M+H)^+$.

Example 16 (54)

6-(2-methoxy-5-(1-methylethyl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.73.

Mass data = 505 $(M+H)^+$.

Example 16 (55)

6-(2-methylthio phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.55.

Mass data = 957 $(2M+H)^+$, 479 $(M+H)^+$.

Example 16 (56)

6-(2,4-difluorophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.58.

Mass data = 937 $(2M+H)^+$, 469 $(M+H)^+$.

Example 16 (57)

6-(2-methyl carbonyl phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.40.

Mass data = 949 $(2M+H)^+$, 475 $(M+H)^+$.

Example 16 (58)

6-(3-carboxy phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.34.

Mass data = 953 $(2M+H)^+$, 477 $(M+H)^+$.

Example 16 (59)

6-(4-dimethylaminophenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.21.

Mass data = 951 $(2M+H)^+$, 476 $(M+H)^+$.

Example 16 (60)

6-(4-(thiophen-2-yl) phenyl)-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 871 $(2M+H)^+$, 439 $(M+H)^+$.

Example 17

6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

A 60 % sodium hydride (12 mg) was suspended in 1,4-dioxane (1.0 mL) and 1,4-dioxane solution (1 mL) of 3,4-dimethoxybenzyl alcohol (25 mg) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 minutes. 1,4-dioxane solution (1 mL) of compound produced in Reference Example 1 (41 mg) was added to the reaction mixture at room

temperature. The reaction mixture was stirred at 100°C for three hours. The reaction mixture was cooled to room temperature and concentrated. The obtained residue was washed with diisopropyl ether (5 mL), and thereafter, 1 N hydrochloric acid (1 mL) was added. It was extracted twice with chloroform (3 mL). The extract was concentrated, and the compound of this invention (26 mg) which had the following physical property values was obtained.

TLC = Rf 0.47 (hexane : ethyl acetate = 1 : 1).
NMR (d6-DMSO)= δ 11.06 (br, 1H), 7.91(s, 1H), 7.84 (8.4 Hz, 2H = d), 7.35 (d, J = 8.4 Hz,2H), 7.15 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 8.1, 1.8 Hz,1H), 6.95 (d, J = 8.1 Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.35 (s, 3H).
HPLC retention time (minutes) = 4.10.
Mass data = 494 $(M+H)^+$.

Examples 17 (1)-17 (63)
Using corresponding alcohol derivatives instead of 3,4-dimethoxybenzyl alcohol, the same operation as in Example 17 was carried out, and following compounds of this invention were obtained.

Example 17 (1)
2-((3-methylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 4.08.
Mass data = 761 $(2M+Na)^+$, 370 $(M+H)^+$.

Example 17 (2)
2-((3-chlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 4.09.
Mass data = 390 $(M+H)^+$.

Example 17 (3)
2-((3-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 3.98.
Mass data = 793 $(2M+ Na)^+$, 386 $(M+H)^+$.

Example 17 (4)
6-bromo-2-((3-methylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 4.34.

Mass data = 448 $(M+H)^+$.

Example 17 (5)

6-bromo-2-((3-chlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.34.

Mass data = 468 $(M+H)^+$.

Example 17 (6)

6-bromo-2-((3-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.22.

Mass data = 466 $(M+H)^+$.

Example 17 (7)

6-bromo-2-((3-trifluoromethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.34.

Mass data = 502 $(M+H)^+$.

Example 17 (8)

2-((2-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.99.

Mass data = 793 $(2M+ Na)^+$, 386 $(M+H)^+$;

NMR (d6-DMSO)= δ 10.88 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H). 7.49 (d, J = 6.6 Hz, 1H), 7.38-7.31(m, 3H), 7.01 (d, J = 7.8 Hz, 1H), 6.97 (td, J = 7.8, 0.9 Hz, 1H), 5.38 (s, 2H), 3.01 (s, 3H), 2.36 (s, 3H).

Example 17 (9)

2-(1-phenylethyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.04.

Mass data = 761 $(2M+Na)^+$, 370 $(M+H)^+$;.

NMR (d6-DMSO)= δ 10.94 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.66 (s, 2H) 7.48 (d, J = 7.2 Hz, 2H), 7.39-7.22 (m, 5H),6.12 (q, J = 6.3 Hz, 1H), 2.36 (s, 3H), 1.59 (d, J = 6.3 Hz, 3H).

Example 17 (10)

2-((furan-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.82.

Mass data = 713 $(2M+Na)^+$, 346 $(M+H)^+$;.

NMR (d6DMSO)= δ 10,88 (s, 1H), 7,86 (d, J = 8,1 Hz, 2H), 7,80-7,73 (m, 3H), 7.36 (d, J = 8.1 Hz,2H), 6.63 (d, J = 3.0 Hz, 1H), 6.51-6.49(m, 1H), 5.35 (s, 2H), 2.3 (s, 3H).

Example 17 (11)

2-((2-methylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.06.

Mass data = 761 $(2M+ Na)^+$, 370 $(M+H)^+$.

Example 17 (12)

2-((2-chlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.10.

Mass data = 390 $(M+H)^+$.

Example 17 (13)

6-bromo-2-((2-phenyl phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.45.

Mass data = 510 $(M+H)^+$.

Example 17 (14)

2-((2-trifluoromethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.11.

Mass data = 869 $(2M+ Na)^+$, 424 $(M+H)^+$.

Example 17 (15)

2-((naphthalen-1-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.15.

Mass data = 733 $(2M+ Na)^+$, 406 $(M+H)^+$.

Example 17 (16)

2-((naphthalen-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.17.

Mass data = 833 $(2M+ Na)^+$, 406 $(M+H)^+$.

Example 17 (17)

2-((2,3-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.95.

Mass data = 853 $(2M+ Na)^+$, 416 $(M+H)^+$.

Example 17 (18)

2-((2,5-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.99.

Mass data = 853 $(2M+ Na)^+$, 416 $(M+H)^+$.

Example 17 (19)

2-((3,5-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.97.

Mass data = 853 $(2M+ Na)^+$, 416 $(M+H)^+$.

Example 17 (20)

2-((2,3-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.21.

Mass data = 424 $(M+H)^+$.

Example 17 (21)

2-((2,4-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.24.

Mass data = 424 $(M+H)^+$.

Example 17 (22)

2-((2,5-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.21.

Mass data = 424 $(M+H)^+$.

Example 17 (23)

2-((2,6-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.19.

Mass data = 424 $(M+H)^+$.

Example 17 (24)

2-((3,4-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.21.

Mass data = 424 $(M+H)^+$.

Example 17 (25)

2-((3,5-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.24.

Mass data = 424 $(M+H)^+$.

Example 17 (26)

2-((4-ethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.17.

Mass data = 789 $(2M+Na)^+$, 384 $(M+H)^+$.

Example 17 (27)

2-((4-(1-methylethyl) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.26.

Mass data = 817 $(2M+ Na)^+$, 398 $(M+H)^+$.

Example 17 (28)

2-((4-[1,1-dimethylethyl] phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.35.

Mass data = 845 $(2M+ Na)^+$, 412 $(M+H)^+$.

Example 17 (29)

2-((4-phenyl phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.26.

Mass data = 885 $(2M+ Na)^+$, 432 $(M+H)^+$.

Example 17 (30)

2-((3-phenoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.26.

Mass data = 917 $(2M+ Na)^+$, 448 $(M+H)^+$.

Example 17 (31)

2-((2-phenyl phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.00.

Mass data = 885 $(2M+ Na)^+$, 432 $(M+H)^+$.

Example 17 (32)

2-((1,3-dioxan indan-4-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.9 5.

Mass data = 821 $(2M+ Na)^+$, 400 $(M+H)^+$.

Example 17 (33)

2-((1,3-dioxan indan-5-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.93.

Mass data = 821 $(2M+ Na)^+$, 400 $(M+H)^+$.

Example 17 (34)

2-((3-trifluoromethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.13.

Mass data = 869 $(2M+ Na)^+$, 424 $(M+H)^+$.

Example 17 (35)

2-((4-methylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.08.

Mass data = 761 $(2M+ Na)^+$, 370 $(M+H)^+$.

Example 17 (36)

2-((4-chlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.10.

Mass data = 801 $(2M+ Na)^+$, 390 $(M+H)^+$.

Example 17 (37)

2-((4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.97.

Mass data = 793 $(2M+ Na)^+$, 386 $(M+H)^+$.

Example 17 (38)

2-((4-trifluoromethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.13.

Mass data = 869 $(2M+ Na)^+$, 424 $(M+H)^+$.

Example 17 (39)

6-bromo-2-((4-methylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.32.

Mass data = 448 $(M+H)^+$.

Example 17 (40)

6-bromo-2-((2-methylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.30.

Mass data = 448 $(M+H)^+$.

Example 17 (41)

6-bromo-2-((2-chlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.32.

Mass data = 468 $(M+H)^+$.

Example 17 (42)

6-bromo-2-((2-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.26.

Mass data = 464 $(M+H)^+$.

Example 17 (43)

6-bromo-2-((2-trifluoromethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.34.

Mass data = 502 $(M+H)^+$.

Example 17 (44)

6-bromo-2-((naphthalen-1-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.37.

Mass data = 482 $(M+H)^+$.

Example 17 (45)

6-bromo-2-((2,3-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.21.

Mass data = 494 $(M+H)^+$.

Example 17 (46)

6-bromo-2-((4-ethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.43.

Mass data = 462 $(M+H)^+$.

Example 17 (47)

6-bromo-2-((4-(1-methylethyl) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.50.

Mass data = 476 $(M+H)^+$.

Example 17 (48)

6-bromo-2-((4-[1,1-dimethylethyl] phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.55.

Mass data = 490 $(M+H)^+$.

Example 17 (49)

6-bromo-2-((1,3-dioxan indan-4-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.19.

Mass data = 478 $(M+H)^+$.

Example 17 (50)

6-bromo-2-((1,3-dioxan indan-5-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.17.

Mass data = 478 $(M+H)^+$.

Example 17 (51)

6-bromo-2-((4-chlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.34.

Mass data = 468 $(M+H)^+$.

Example 17 (52)

6-bromo-2-((4-methoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.22.

Mass data = 464 $(M+H)^+$.

Example 17 (53)

6-bromo-2-((4-trifluoromethylphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.35.

Mass data = 502 $(M+H)^+$.

Example 17 (54)

6-bromo-2-((naphthalen-2-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.41.

Mass data = 484 $(M+H)^+$.

Example 17 (55)

6-bromo-2-((2,5-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.22.

Mass data = 494 $(M+H)^+$.

Example 17 (56)

6-bromo-2-((3,5-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.22.

Mass data = 494 $(M+H)^+$.

Example 17 (57)

6-bromo-2-((2,3-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.43.

Mass data = 502 $(M+H)^+$.

Example 17 (58)

6-bromo-2-((2,4-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.45.

Mass data = 502 $(M+H)^+$.

Example 17 (59)

6-bromo-2-((2,5-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.43.

Mass data = 502 $(M+H)^+$.

Example 17 (60)

6-bromo-2-((2,6-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.45.

Mass data = 502 $(M+H)^+$.

Example 17 (61)

6-bromo-2-((3,4-dichlorophenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.43.

Mass data = 502 $(M+H)^+$.

Example 17 (62)

6-bromo-2-((4-phenyl phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.50.

Mass data =510 $(M+H)^+$.

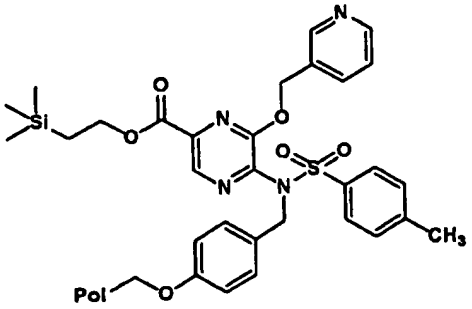
Example 17 (63)

6-bromo-2-((3-phenoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.46.

Mass data = 526 $(M+H)^+$.

Reference Example 12

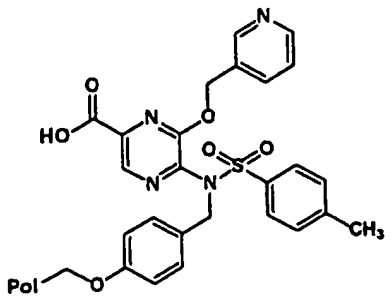


(5)

Triethylamine (0.948 mL), 2-(trimethylsilyl)-ethanol (0.487 mL), dichlorobis (triphenyl phosphine) palladium (II) (96 mg) were successively added to dimethylsulfoxide (10 mL) suspension of compound (4) produced in Reference Example 11 (1.0 g) at room temperature. The reaction liquor was stirred under carbon monoxide at 80°C for 24 hours. The reaction mixture was cooled to room temperature and was filtered. The obtained resin was washed

successively three times with dimethylsulfoxide (30 mL), three times with tetrahydrofuran (30 mL), and three times with methylene chloride (30 mL) and was dried, and compound (5) (1.03 g) was obtained.

Reference Example 13

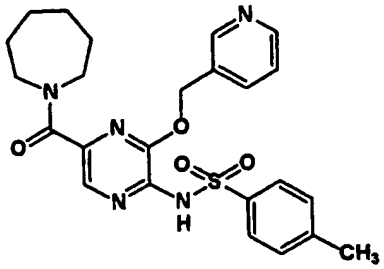


(6)

Tetrahydrofuran solution (5 mL) of 1 M fluorinated tetrabutyl ammonium was added to tetrahydrofuran (5 mL) suspension of compound (5) produced in Reference Example 12 (500 mg) at room temperature. The reaction mixture was stirred at room temperature for one hour. The reaction mixture was filtered. The obtained resin was successively washed three times with tetrahydrofuran (20 mL), three times with 0.2 N hydrochloric acid and tetrahydrofuran liquid mixture (1 : 2) (20 mL), three times with water and tetrahydrofuran liquid mixture (1 : 2) (20 mL), three times with tetrahydrofuran (20 mL), and three times with methylene chloride (20 mL) and was dried, and compound (6) (490 mg) was obtained.

Example 18

6-(perhydroazepin-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.



Homo piperidine (0.186 mL), N,N-diisopropyl ethylamine (0.575 mL), hexafluoro phosphonic acid benzotriazol-1-yl-1-oxy-tris (pyrrolidino) phosphonium (859 mg) were added successively to N,N-dimethylformamide (5 mL) suspension of compound (6) produced in Reference Example 13 (490 mg). The reaction mixture was stirred at room temperature for four hours. The reaction mixture was filtered. Homo piperidine (0.186 mL), N,N-diisopropyl ethylamine (0.575 mL), hexafluoro phosphonic acid benzotriazol-1-yl-1-oxy-tris (pyrrolidino) phosphonium (859 mg)

were added successively to N,N-dimethylformamide (5 mL) suspension of the obtained resin. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered. The obtained resin was washed five times with N,N-dimethylformamide (20 mL) and five times with methylene chloride (20 mL). Using methylene chloride solution of 50 % trifluoroacetic acid instead of 1,2-dichloromethane solution of 50 % trifluoroacetic acid, the same operation as in Example 14 was carried out for the obtained resin, and the compound of this invention (167 mg) which had the following physical property values was obtained.

TLC = Rf 0.66 (chloroform : methanol = 10 : 1).
NMR (d6-DMSO)= δ 8.57 (br, 1H), 8.49 (d, J = 3.9 Hz, 1H), 7.65 (7.8 Hz, 2H = d), 7.34 (m, 3H), 6.92 (d, J = 7.8 Hz, 2H), 5.26 (s, 2H), 3.49 (m, 4H), 2.37 (s, 3H), 1.60 (m, 4H), 1.41 (m, 4H).
HPLC retention time (minutes) = 3.22.
Mass data = 963 $(2M+H)^+$, 482 $(M+H)^+$.

Examples 18 (1)-18 (77).
Using corresponding amine derivatives instead of homo piperidine, the same operation as in Example 18 was carried out, and following compounds of this invention were obtained.

Example 18 (1)
6-cyclobutyl aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 3.26.
Mass data = 907 $(2M+H)^+$, 454 $(M+H)^+$.

Example 18 (2)
6-cyclopentyl aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 3.33.
Mass data = 935 $(2M+H)^+$, 468 $(M+H)^+$.

Example 18 (3)
6-cyclohexyl aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 3.40.
Mass data = 963 $(2M+H)^+$, 482 $(M+H)^+$.

Example 18 (4)

6-(5-methylisoxazol-3-yl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.36.

Mass data = 961 $(2M+H)^+$, 481 $(M+H)^+$.

Example 18 (5)

6-(pyrrolidine-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.18.

Mass data = 907 $(2M+H)^+$, 454 $(M+H)^+$.

Example 18 (6)

6-(3-hydroxypyrrolidine-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.07.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (7)

6-(1,3-thiazolin-2-yl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.14.

Mass data = 969 $(2M+H)^+$, 485 $(M+H)^+$.

Example 18 (8)

6-((tetrahydrofuran-2-yl) methyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.20.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (9)

6-(4-methylpiperazine-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.01.

Mass data = 965 $(2M+H)^+$, 483 $(M+H)^+$.

Example 18 (10)

6-(morpholin-4-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.14.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (11)

6-(thio morpholin-4-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.25.

Mass data = 971 $(2M+H)^+$, 486 $(M+H)^+$.

Example 18 (12)

6-(pyridin-3-yl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.09.

Mass data = 953 $(2M+H)^+$, 477 $(M+H)^+$.

Example 18 (13)

6-(pyridin-4-yl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.10.

Mass data = 477 $(M+H)^+$.

Example 18 (14)

6-(1,1-dimethylethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.32.

Mass data = 456 $(M+H)^+$.

Example 18 (15)

6-(1,2-dimethylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.36.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (16)

6-(1-methyl-2-methoxyethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.20.

Mass data = 943 $(2M+H)^+$, 472 $(M+H)^+$.

Example 18 (17)

6-(1,3-dimethylbutyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.47.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (18)

6-(1-methylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.31.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 18 (19)

6-(1-ethyl propyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.36.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (20)

6-(1-methylbutyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.40.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (21)

6-(2,2-dimethylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.36.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (22)

6-(2-hydroxypropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.09.

Mass data = 915 $(2M+H)^+$, 458 $(M+H)^+$.

Example 18 (23)

6-(2-methylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.29.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 18 (24)

6-(2-fluoroethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 891 $(2M+H)^+$, 446 $(M+H)^+$.

Example 18 (25)

6-(2-acetylamino ethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.09.

Mass data = 969 $(2M+H)^+$, 485 $(M+H)^+$.

Example 18 (26)

6-(2-methoxyethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 915 $(2M+H)^+$, 458 $(M+H)^+$.

Example 18 (27)

6-pentyl aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (28)

6-dimethylaminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.12.

Mass data = 855 $(2M+H)^+$, 428 $(M+H)^+$.

Example 18 (29)

6-diethylamino carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.25.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 18 (30)

6-(N-methyl-N-propylamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.27.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 18 (31)

6-dipropylamino carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.41.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (32)

6-butylamino carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.32.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 18 (33)

6-ethylamino carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 855 $(2M+H)^+$, 428 $(M+H)^+$.

Example 18 (34)

6-(3-hydroxypiperidine-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.09.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (35)

6-(N-methyl-N-[2-methylpropyl] amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.31.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (36)

6-(N-methyl-N-pentyl amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.44.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (37)

6-(N-methyl-N-[1-methylethyl] amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.25.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 18 (38)

6-(1-methylethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.23.

Mass data = 883 $(2M+H)^+$, 442 $(M+H)^+$.

Example 18 (39)

6-(pyrazol-3-yl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.18.

Mass data = 931 $(2M+H)^+$, 466 $(M+H)^+$.

Example 18 (40)

6-(1,2,3,6-tetrahydropyridin-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.27.

Mass data = 931 $(2M+H)^+$, 466 $(M+H)^+$.

Example 18 (41)

6-(pyrimidine-4-yl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.22.

Mass data = 933 $(2M+H)^+$, 478 $(M+H)^+$.

Example 18 (42)

6-((1R)-1-hydroxymethyl-2-methylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.22.

Mass data = 971 $(2M+H)^+$, 486 $(M+H)^+$.

Example 18 (43)

6-((1R)-1-methyl-2-hydroxyethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.11.

Mass data = 915 $(2M+H)^+$, 458 $(M+H)^+$.

Example 18 (44)

6-(N-ethyl-N-(2-hydroxyethyl amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.01.

Mass data = 943 $(2M+H)^+$, 472 $(M+H)^+$.

Example 18 (45)

6-(3-pyrrolinyl-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.18.

Mass data = 903 $(2M+H)^+$, 452 $(M+H)^+$.

Example 18 (46)

6-(2-hydroxymethyl pyrrolidinyl-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.11.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (47)

6-(2-methylpiperidin-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 963 $(2M+H)^+$, 482 $(M+H)^+$.

Example 18 (48)

6-(3-methylpiperidin-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 963 $(2M+H)^+$, 482 $(M+H)^+$.

Example 18 (49)

6-(4-methylpiperidin-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.36.

Mass data = 963 $(2M+H)^+$, 482 $(M+H)^+$.

Example 18 (50)

6-(1,1-dimethylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.39.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (51)

6-(1-hydroxymethyl propylamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 943 $(2M+H)^+$, 472 $(M+H)^+$.

Example 18 (52)

6-(2-methylbutyl amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (53)

6-(2-dimethylaminoethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.00.

Mass data = 941 $(2M+H)^+$, 471 $(M+H)^+$.

Example 18 (54)

6-(2-hydroxyethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.07.

Mass data = 887 $(2M+H)^+$, 444 $(M+H)^+$.

Example 18 (55)

6-(2-propynyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.22.

Mass data = 875 $(2M+H)^+$, 438 $(M+H)^+$.

Example 18 (56)

6-(2-propenyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.22.

Mass data = 879 $(2M+H)^+$, 440 $(M+H)^+$.

Example 18 (57)

6-(3-methyl butyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.40.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (58)

6-(3-dimethylaminopropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.01.

Mass data = 969 $(2M+H)^+$, 485 $(M+H)^+$.

Example 18 (59)

6-(3-ethoxy propyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.23.

Mass data = 971 $(2M+H)^+$, 486 $(M+H)^+$.

Example 18 (60)

6-hexyl aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.51.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (61)

6-(N,N-bis [2-propenyl] amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4m methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.35.

Mass data = 959 $(2M+H)^+$, 480 $(M+H)^+$.

Example 18 (62)

6-(N-methyl-N-butylamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.34.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (63)

6-(N-ethyl-N-butylamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (64)

6-(N-methyl-N-hydroxyamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.11.

Mass data = 859 $(2M+H)^+$, 430 $(M+H)^+$.

Example 18 (65)

6-(3-methoxy propyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 943 $(2M+H)^+$, 472 $(M+H)^+$.

Example 18 (66)

6-(N-methyl-N-(2-dimethylaminoethyl amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.00.

Mass data = 969 $(2M+H)^+$, 485 $(M+H)^+$.

Example 18 (67)

6-(N-ethyl-N-[1-methylethyl] amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.31.

Mass data = 939 $(2M+H)^+$, 470 $(M+H)^+$.

Example 18 (68)

6-(N-(1-hydroxyethyl)-N-(1-methylethyl) amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.05.

Mass data = 971 $(2M+H)^+$, 486 $(M+H)^+$.

Example 18 (69)

6-((1S)-1-hydroxymethyl-2-methylpropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.20.

Mass data = 971 $(2M+H)^+$, 486 $(M+H)^+$.

Example 18 (70)

6-((2R)-2-hydroxymethyl pyrrolidin-1-yl) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.12.

Mass data = 967 $(2M+H)^+$, 484 $(M+H)^+$.

Example 18 (71)

6-((2R)-2-hydroxypropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.11.

Mass data = 915 $(2M+H)^+$, 458 $(M+H)^+$.

Example 18 (72)

6-((2S)-2-hydroxypropyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.11.

Mass data = 915 $(2M+H)^+$, 458 $(M+H)^+$.

Example 18 (73)

6-(N-ethyl-N-methylamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.18.

Mass data = 883 $(2M+H)^+$, 442 $(M+H)^+$.

Example 18 (74)

6-(2,2,2, trifluoroethyl) aminocarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.33.

Mass data = 963 $(2M+H)^+$, 482 $(M+H)^+$.

Example 18 (75)

6-(N-[2-hydroxyethyl]-N-propylamino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.05.

Mass data = 971 $(2M+H)^+$, 486 $(M+H)^+$.

Example 18 (76)

6-(N-methyl-N-[2-methoxyethyl] amino) carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.16.

Mass data = 943 $(2M+H)^+$, 472 $(M+H)^+$.

Example 18 (77)

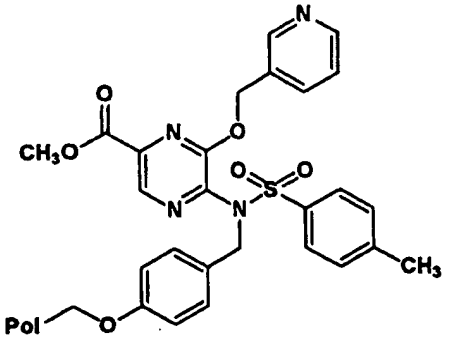
6-benzylamino carbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.38.

Mass data = 979 $(2M+H)^+$, 490 $(M+H)^+$;.

NMR (d6-DMSO)= δ 11.60-11.20 (br, 1H), 9.10 (t, J = 6.3 Hz,1H), 8.80 (s, 1H), 8.56 (d, J = 3.6 Hz, 1H), 8.24 (s, 1H), 7.98 (dt, J = 6.9, 1.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.45-7.08 (m, 8H), 5.61 (s, 2H), 4.48 (d, J = 6.3 Hz, 2H), 2.35 (S, 3H).

Reference Example 14.

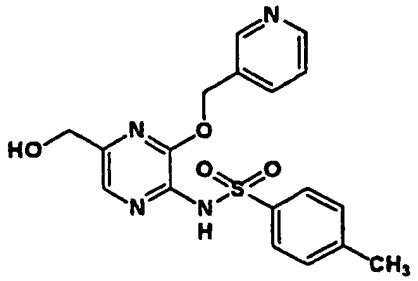


(7)

Thw same operation as in Reference Example 12 was carried out using methanol instead of 2-(trimethylsilyl) ethanol, and compound (7) was obtained.

Example 19

6-hydroxymethyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.



Compound (7) produced in Reference Example 14 (400 mg) was added at room temperature to tetrahydrofuran solution (2 mL) of 2 M lithium borohydride. The reaction mixture was stirred at room temperature for two hours. The reaction mixture was filtered. The obtained resin was successively washed five times with methanol (3 mL), five times with tetrahydrofuran (3 mL), and five times with 1,2-dichloromethane (3 mL), and thereafter, the same operation as in Example 14 was carried out, and the compouns of this invention (41 mg) which had the following physical property values was obtained.

HPLC retention time (minutes) = 3.07.

Mass data = 773 $(2M+H)^+$, 387 $(M+H)^+$.

Example 20

6-methyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

[1,3-bis (diphenylphosphino) propane] dichloro nickel (II) (109 mg) was added to anhydrous tetrahydrofuran (5 mL) suspension of compound (4) produced in Reference Example 11 (300 mg) at room temperature. The reaction mixture was cooled to 0°C and tetrahydrofuran solution (1.11 mL) of 0.93 M bromomethane magnesium was added. The reaction mixture was stirred at room temperature for six hours. The reaction mixture was filtered. The obtained resin was successively washed five times with methanol (5 mL), five times with tetrahydrofuran (5 mL), and five times with 1,2-dichloromethane (3 mL), and thereafter, the same operation as in Example 14 was carried out, and the compound of this invention (100 mg) which had the following physical property values was obtained.

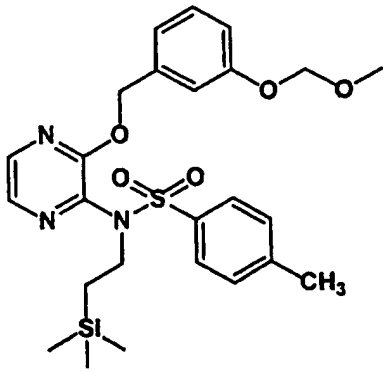
NMR (D20 : CD3CN = 55:45): δ 8.50 (s, 1H), 8.40 (d, J = 5.0 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.35 (dd, J = 7.5, 5.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 5.29 (s, 2H), 2.26 (s, 3H), 2.19 (s, 3H).

HPLC retention time (minutes) = 3.23.

Mass data = 741 $(2M+H)^+$, 371 $(M+H)^+$.

Reference Example 15

2-((3-(methoxymethyl oxy) phenyl) methyl oxy)-3-(N-(4-methylphenyl sulfonyl)-N-(2-trimethylsilyl ethyl) amino) pyrazine.



Using the compound obtained in Example 3 (4) (1.3 g), the same operation as in Reference Example 4 was carried out, and the title compound (843 mg) which had the following physical property values was obtained.

TLC = Rf 0.75 (hexane : ethyl acetate = 1 : 1).
NMR (d6-DMSO)= δ 8.25 (d, J = 2.7 Hz, 1H), 8.16 (d, J = 2.7 Hz,1H), 7.69 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.11 (s, 1H), 7.06 (d, J = 7.5 Hz,1H), 6.99 (d, J = 7.5 Hz, 1H), 5.40 (s, 2H), 5.19 (s, 2H), 3.57-3.50 (m, 2H), 3.36 (s, 3H), 2.38 (s, 3H), 0.50-0.43 (m, 2H), -0.14 (s, 9H).

Reference Example 16

2-((3-hydroxyphenyl) methyl oxy)-3-(N-(4-methylphenyl sulfonyl)-N-(2-trimethylsilyl ethyl) amino) pyrazine.

Water (5.5 mL) was added to acetic acid (5.5 mL) solution of compound produced in Reference Example 15 (820 mg). The reaction mixture was stirred at 90°C for three hours. The reaction mixture was cooled to room temperature and concentrated. The obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and the title compound (756 mg) which had the following physical property values was obtained.

TLC : Rf 0.34 (hexane : ethyl acetate = 1 : 1).
NMR ($CDCl_3$)= δ 8.25 (2.7 Hz = d, 1H), 8.14 (d, J = 2.7 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 6.85-6.82 (m, 2H), 6.75-6.72 (m, 1H), 5.34 (s, 2H), 3.57-3.49 (m, 2H), 2.39 (s, 3H), 0.50-0.40 (m, 2H), -0.14 (s, 9H).

Example 21

2-((3-ethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

Ethanol (0.011 mL), polymer support / triphenyl phosphine (1,34 mmol/g, 143 mg), toluene

solution (0.087 mL) of 40 % diethyl azodicarboxylate ester were added successively to tetrahydrofuran (2 mL) solution of compound produced in Reference Example 16 (30 mg) at 0°C. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered, and the obtained resin was washed with tetrahydrofuran (1 mL). Filtrate and lavage were mixed. 5 N sodium hydroxide aqueous solution (1 mL) was added to the mixed liquid, and the mixture was stirred at room temperature for 30 minutes. Water (1 mL) was added to the reaction mixture, and thereafter, it was extracted twice with chloroform (3 mL). The liquid extract was dried with magnesium sulfate and concentrated. Tetrahydrofuran solution (0.106 mL) of 1.0M fluorinated tetrabutyl ammonium was added to tetrahydrofuran (1.5 mL) solution of the obtained residue (23 mg). The reaction mixture was stirred at room temperature for 17 hours. Water (1.5 mL) was added to the reaction mixture, and thereafter, it was extracted twice with chloroform (3 mL). The liquid extract was dried with magnesium sulfate, it was concentrated, and the title compound (17 mg) which had the following physical property values was obtained.

TLC = Rf 0.73 (hexane : ethyl acetate = 1 : 1).
NMR (D2O : CD3CN = 40:60, 50°C): δ 7.80 (d, J = 8.5 Hz, 2H), 7.59 (m, 2H), 7.28 (d, J = 8, 5 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.93 (m, 2H), 6.83 (8.0 Hz = d, 1H), 5.30 (2H), 3.99 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H).
HPLC retention time (minutes) = 4.06.
Mass data = 799 $(2M+H)^+$, 400 $(M+H)^+$.

Examples 21. (1)-21 (7).
Using corresponding alcohol derivatives instead of ethanol, the same operation as in Example 21 was carried out, and following compounds of this invention were obtained.

Example 21 (1)
2-((3-(1-methyl ethoxy) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 4.45.
Mass data = 827 $(2M+H)^+$, 428 $(M+H)^+$.

Example 21 (2)
2-((3-(2-methylpropyl oxy) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.
HPLC retention time (minutes) = 4.32.
Mass data = 855 $(2M+H)^+$, 428 $(M+H)^+$.

Example 21 (3)

2-((3-butyloxy phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.32.

Mass data = 855 $(2M+H)^+$, 428 $(M+H)^+$.

Example 21 (4)

2-((3-(4-methoxybutyl oxy) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 4.10.

Mass data = 915 $(2M+H)^+$, 458 $(M+H)^+$.

Example 21 (5)

2-((3-(3-dimethylaminopropyl oxy) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.42.

Mass data = 457 $(M+H)^+$.

Example 21 (6)

2-((3-[tetrahydropyran-4-yloxy] phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.95.

Mass data = 911 $(2M+H)^+$, 456 $(M+H)^+$.

Example 21 (7)

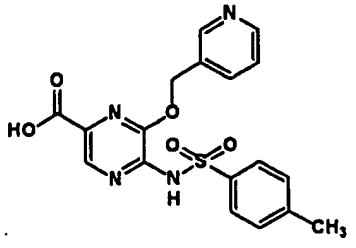
2-((3-(2-[piperidine-1-yl] ethyl oxy) phenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

HPLC retention time (minutes) = 3.47.

Mass data = 483 $(M+H)^+$.

Example 22

6-carboxy-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.



Compound (6) produced in Reference Example 13 (110 mg) was added to tetrahydrofuran

solution (1 mL) of 1 M fluorinated tetrabutyl ammonium. The reaction mixture was stirred at room temperature for one hour. The reaction mixture was filtered. The obtained resin was washed five times with tetrahydrofuran (3 mL) and five times with 1,2-dichloromethane (3 mL). The same operation as in Example 14 was carried out with the obtained resin, and the title compound (25 mg) which had the following physical property values was obtained.

TLC = Rf 0.37 (chloroform : methanol : acetic acid = 9:1:0.5).
HPLC retention time (minutes) = 3.14.
Mass data = 801 $(2M+H)^+$, 401 $(M+H)^+$;.
NMR (d6DMSO)= δ 8.72 (s, 1H), 8.51 (d, J = 3.3 Hz, 1H), 8.03 (s, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.38 (dd, J = 7.5, 4.8 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 5.29 (s, 2H), 2.27 (s, 3H).

Example 23

6-methoxycarbonyl-2-((pyridin-3-yl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine.

The same operation as in Example 14 was carried out using methylene chloride solution of 25 % trifluoroacetic acid instead of 1,2-dichloromethane solution of 50 % trifluoroacetic acid, and also using compound (7) produced in Reference Example 14, the title compound (120 mg) which had the following physical property values was obtained.

TLC : Rf 0.66 (chloroform : methanol : acetic acid = 9:1:0.5).
HPLC retention time (minutes) = 3.23.
Mass data = 829 $(2M+H)^+$, 415 $(M+H)^+$;.
NMR ($CDCl_3$)= δ 8.71 (d, J = 1.5 Hz, 1H), 8.62 (dd, J = 4.8, 1.5 Hz, 1H), 8.52 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.84 (dt, J = 8.4, 1.8 Hz, 1H), 7.37-7.26 (m, 3H), 5.48 (s2H), 3.94 (s, 3H), 2.41 (s, 3H).

Examples 24. (1)-24 (114).

Using corresponding sulphonyl chloride instead of 4-chlorobenzene sulphonyl chloride, and also using corresponding benzyl alcohol instead of 3,4-dimethoxybenzyl alcohol, the same operation as in Reference Example 6 to Example 7 was carried out, and the compounds of this invention shown below were obtained.

Example 24 (1)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 3-dichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.26.

Mass data = 492, 490, 488 $(M+H)^+$.

Example 24 (2)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-chloro-2-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.32.

Mass data = 472, 470, 468 $(M+H)^+$.

Example 24 (3)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-(trifluoromethyl) benzenesulphonamide.

HPLC retention time (minutes) = 4.17.

Mass data = 490, 488 $(M+H)^+$.

Example 24 (4)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-chlorobenzenesulphonamide.

HPLC retention time (minutes) = 4.11.

Mass data = 458, 456, 454 $(M+H)^+$.

Example 24 (5)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-bromo benzenesulphonamide.

HPLC retention time (minutes) = 4.15.

Mass data = 502, 500, 498 $(M+H)^+$.

Example 24 (6)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-chloro-4-fluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.17.

Mass data = 476, 474, 472 $(M+H)^+$.

Example 24 (7)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,5-dichloro-4-nitro-3-thiophene sulfonamide.

HPLC retention time (minutes) = 4.28.

Mass data = 543, 541, 539 $(M+H)^+$, 317, 214.

Example 24 (8)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,6-dichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.21.

Mass data = 492, 490, 488 $(M+H)^+$.

Example 24 (9)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-bromo benzenesulphonamide.

HPLC retention time (minutes) = 4.28.

Mass data = 502, 500, 498 $(M+H)^+$.

Example 24 (10)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 4-difluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.12.

Mass data = 458, 456 $(M+H)^+$.

Example 24 (11)

N-{5-bromo-3-[(6-methoxy-3-pyridinyl) methoxy]-2-pyrazinyl)-4-methylbenzene sulfonamide.

TLC = Rf 0.35 (hexane : ethyl acetate = 2 : 1).

NMR ($CDCl_3$)= δ 2.41 (s, 3H), 3.96 (s, 3H), 5.31 (s, 2H), 6.79 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.49 (s, 1H), 7.66 (dd, J = 8.5, 2-5 Hz,1H), 7.86 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 2.5 Hz,1H).

Mass data = 931 $(2M+H)^+$, 467, 465 $(M+H)^+$.

Example 24 (12)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.15.

Mass data = 436, 434 $(M+H)^+$.

Example 24 (13)

N-{5-bromo-3-[(2-methoxy-3-pyridinyl) methoxy]-2-pyrazinyl)-4-methylbenzene sulfonamide.

TLC = Rf 0.35 (hexane : ethyl acetate = 2 : 1).

NMR ($CDCl_3$)= δ 2.42 (s, 3H), 3.99 (s, 3H), 5.37 (s, 2H), 6.92 (dd, J = 7.0, 5.0 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.57 (s, 1H), 7.64 (dd, J = 7.0, 2.0 Hz, 1H), 7.85 (s, 1H), 7.99 (d, J = 8.5 Hz, 2H), 8.20 (dd, J = 5.0, 2.0 Hz, 1H).

Mass data = 467, 465 $(M+H)^+$.

Example 24 (14)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-chloro-4-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.30.

Mass data = 472, 470, 468 $(M+H)^+$.

Example 24 (15)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-chlorobenzene sulphonamide.

HPLC retention time (minutes) = 4.19.

Mass data = 458, 456, 454 $(M+H)^+$.

Example 24 (16)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-fluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.04.

Mass data = 440, 438 $(M+H)^+$.

Example 24 (17)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,3,4-trichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.44.

Mass data = 528, 526, 524, 522 $(M+H)^+$.

Example 24 (18)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 4-dichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.30.

Mass data = 492, 490, 488 $(M+H)^+$.

Example 24 (19)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 6-difluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.00.

Mass data = 458, 456 $(M+H)^+$.

Example 24 (20)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-cyanobenzene sulfonamide.

HPLC retention time (minutes) = 4.00.

Mass data = 447, 445 $(M+H)^+$.

Example 24 (21)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-fluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.10.

Mass data = 440, 438 $(M+H)^+$.

Example 24 (22)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,4,6-trichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.39.

Mass data = 528, 526, 524, 522 $(M+H)^+$.

Example 24 (23)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-thiophene sulfonamide.

TLC: Rf 0.27 (toluene : ethyl acetate = 15 : 1).

NMR ($CDCl_3$)= δ 5.39 (s, 2H), 7.08 (dd, J = 5.0, 4.0 Hz, 1H), 7.42 (m, 5H), 7.61 (s, 1H), 7.63 (dd J = 5.0, 1.5 Hz, 1H), 7.91 (dd, J = 4.0, 1.5 Hz, 1H), 7.94 (s, 1H).

Mass data = (APCI, Pos, 40 V) 428, 426 $(M+H)^+$, 384, 382, 281, 279.

Example 24 (24)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl] benzene sulphonamide.

HPLC retention time (minutes) = 4.06.

Mass data = 422, 420 $(M+H)^+$.

Example 24 (25)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-methyl-3-nitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.15.

Mass data = 481, 479 $(M+H)^+$.

Example 24 (26)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-nitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.13.

Mass data = 467, 465 $(M+H)^+$.

Example 24 (27)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 5-dichloro-3-thiophene sulfonamide.

TLC = Rf 0.49 (toluene : ethyl acetate = 6 : 1).

NMR ($CDCl_3$)= δ 5,42 (s, 2H), 7.33 (s, 1H), 7.43 (m, 5H), 7.71 (s, 1H), 7.87 (s, 1H).

Mass data = (FAB, Pos) 500, 498, 496, 494 $(M+H)^+$.

Example 24 (28)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-bromo benzenesulphonamide.

HPLC retention time (minutes) = 4.26.

Mass data = 502, 500, 498 $(M+H)^+$.

Example 24 (29)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.13.

Mass data = 436, 434 $(M+H)^+$.

Example 24 (30)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-bromo-2,5-difluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.26.

Mass data = 538, 536, 534 $(M+H)^+$.

Example 24 (31)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-(trifluoromethyl) benzenesulphonamide.

HPLC retention time (minutes) = 4.24.

Mass data = 490, 488 $(M+H)^+$.

Example 24 (32)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-ethyl benzene sulfonamide.

HPLC retention time (minutes) = 4.22.

Mass data = 450, 448 $(M+H)^+$.

Example 24 (33)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-1-benzothiophene-3-sulfonamide.

HPLC retention time (minutes) = 4.22.

Mass data = 478, 476 $(M+H)^+$, 214.

Example 24 (34)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-(trifluoromethoxy) benzenesulphonamide.

HPLC retention time (minutes) = 4.21.

Mass data = 506, 504 $(M+H)^+$.

Example 24 (35)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-methoxybenzene sulfonamide.

HPLC retention time (minutes) = 4.08.

Mass data = 452, 450 $(M+H)^+$.

Example 24 (36)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-(trifluoromethyl) benzenesulphonamide.

TLC : Rf 0.42 (hexane : ethyl acetate = 4 : 1).

NMR (d6-DMSO)= δ 5.37 (s, 2H), 7.38 (m, 3H), 7.52 (m, 2H), 7.93 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H), 11.42 (s, 1H).

Mass data = 490, 488 $(M+H)^+$.

Example 24 (37)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 4-dichloro-6-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.54.

Mass data = 506,504, 502 $(M+H)^+$.

Example 24 (38)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-chloro-4-(trifluoromethyl) benzene sulphonamide.

HPLC retention time (minutes) = 4.37.

Mass data = 526, 524, 522 $(M+H)^+$.

Example 24 (39)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4, 5-dichloro-2-thiophene sulfonamide.

TLC = Rf 0.24 (hexane : ethyl acetate = 4 : 1).

NMR ($CDCl_3$)= δ 5.40 (s, 2H), 7.42 (m, 5H), 7.65 (s, 1H), 7.68 (s, 1H), 7.98 (s, 1H).

Mass data = (FAB, Pos) 500, 498, 496, 494 $(M+H)^+$.

Example 24 (40)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-fluoro-2-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.19.

Mass data = 454, 452 $(M+H)^+$.

Example 24 (41)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-chloro-3-nitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.21.

Mass data = 503, 501, 499 $(M+H)^+$.

Example 24 (42)

2-({[3-(benzyloxy)-5-bromo-2-pyrazinyl] amino) sulfonyl) methyl benzoate ester.

HPLC retention time (minutes) = 4.11.

Mass data = 480, 478 $(M+H)^+$.

Example 24 (43)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-1-benzothiophene-2-sulfonamide.

HPLC retention time (minutes) = 4.24.

Mass data = 478, 476 $(M+H)^+$, 214.

Example 24 (44)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,4,6-trimethyl benzenesulphonamide.

HPLC retention time (minutes) = 4.39.

Mass data = 464, 462 $(M+H)^+$.

Example 24 (45)

N-(3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 5-dichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.28.

Mass data = 492, 490, 488 $(M+H)^+$.

Example 24 (46)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-(trifluoromethoxy) benzenesulphonamide.

HPLC retention time (minutes) = 4.26.

Mass data = 506, 504 $(M+H)^+$.

Example 24 (47)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,4,5-trichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.48.

Mass data = 528, 526, 524, 522 $(M+H)^+$.

Example 24 (48)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-methyl-2-(trifluoromethyl)-3-furan sulfonamide.

HPLC retention time (minutes) = 4.30.

Mass data = 494, 492 $(M+H)^+$, 214, 158.

Example 24 (49)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-methoxy-4-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.08.

Mass data = 466, 464 $(M+H)^+$.

Example 24 (50)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-methoxy-2-nitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.11.

Mass data = 497, 495 $(M+H)^+$.

Example 24 (51)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-nitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.10.

Mass data = 467, 465 $(M+H)^+$.

Example 24 (52)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-chloro-2,5-dimethylbenzene sulfonamide.

HPLC retention time (minutes) = 4.44.

Mass data = 486, 484, 482 $(M+H)^+$.

Example 24 (53)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 5-dimethyl-3-thiophene sulfonamide.

HPLC retention time (minutes) = 4.22.

Mass data = 456, 454 $(M+H)^+$, 265, 214.

Example 24 (54)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-biphenyl sulfonamide.

HPLC retention time (minutes) = 4.37.

Mass data = 498, 496 $(M+H)^+$.

Example 24 (55)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-methyl-5-nitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.15.

Mass data = 481, 479 $(M+H)^+$.

Example 24 (56)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-bromo-2-methoxybenzene sulfonamide.

HPLC retention time (minutes) = 4.19.

Mass data = 532, 530, 528 $(M+H)^+$.

Example 24 (57)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3, 5-dimethylbenzene sulfonamide.

HPLC retention time (minutes) = 4.26.

Mass data = 450, 448 $(M+H)^+$.

Example 24 (58)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-chloro-2-methoxybenzene sulfonamide.

HPLC retention time (minutes) = 4.19.

Mass data = 488, 486, 484 $(M+H)^+$.

Example 24 (59)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-methoxybenzene sulfonamide.

TLC : Rf 0.25 (hexane : ethyl acetate = 4 : 1).

NMR (d6-DMSO)= δ 3.81 (s, 3H), 5.36 (s, 2H), 7.07 (d, J = 9.0 Hz, 2H), 7.38 (m, 3H), 7.53 (m, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.93 (s, 1H), 11.02 (s, 1H).

Mass data = 452, 450 $(M+H)^+$.

Example 24 (60)

4-acetyl-N-[3-(benzyloxy)-5-bromo-2-pyrazinyl] benzenesulphonamide.

HPLC retention time (minutes) = 4.02.

Mass data = 464, 462 $(M+H)^+$.

Example 24 (61)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-phenoxy benzenesulphonamide.

HPLC retention time (minutes) = 4.39.

Mass data = 514, 512 $(M+H)^+$.

Example 24 (62)

3-[4-({[3-(benzyloxy)-5-bromo-2-pyrazinyl] amino) sulfonyl) phenyl] propanoate methyl ester.

HPLC retention time (minutes) = 4.06.

Mass data = 508, 506 $(M+H)^+$.

Example 24 (63)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-cyanobenzene sulfonamide.

HPLC retention time (minutes) = 4.04.

Mass data = 447, 445 $(M+H)^+$.

Example 24 (64)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-(difluoromethoxy) benzene sulphonamide.

HPLC retention time (minutes) = 4.10.

Mass data = 488, 486 $(M+H)^+$.

Example 24 (65)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-isopropyl benzene sulfonamide.

HPLC retention time (minutes) = 4.32.

Mass data = 464, 462 $(M+H)^+$.

Example 24 (66)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(dimethylamino)-1-naphthalenesulfonamide.

HPLC retention time (minutes) = 3.95.

Mass data = 515, 513 $(M+H)^+$.

Example 24 (67)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-fluoro-3-methyl-1-benzothiophene-2-sulfonamide.

HPLC retention time (minutes) = 4.28.

Mass data = 510, 508 $(M+H)^+$, 317, 214.

Example 24 (68)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-cyanobenzene sulfonamide.

TLC : Rf 0.18 (hexane : ethyl acetate = 4 : 1).

NMR (d6-DMSO)= δ 5.36 (s, 2H), 7.39 (m, 3H), 7.52 (m, 2H), 7.93 (s, 1H), 8.05 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 11.55 (s, 1H).

Mass data = 447, 445 $(M+H)^+$, 214.

Example 24 (69)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-naphthalenesulfonamide.

HPLC retention time (minutes) = 4.24.

Mass data = 472, 470 $(M+H)^+$.

Example 24 (70)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-(1,1-dimethylpropyl) benzenesulphonamide.

HPLC retention time (minutes) = 4.48.

Mass data = 492, 490 $(M+H)^+$.

Example 24 (71)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-chloro-3-methyl-1-benzothiophene-2-sulfonamide.

HPLC retention time (minutes) = 4.43.

Mass data = 528, 526, 524 $(M+H)^+$, 317, 214, IS8.

Example 24 (72)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,3,5,6-tetramethyl benzenesulphonamide.

HPLC retention time (minutes) = 4.46.

Mass data = 478, 476 $(M+H)^+$.

Example 24 (73)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 5-dimethylbenzene sulfonamide.

HPLC retention time (minutes) = 4.24.

Mass data = 450, 448 $(M+H)^+$.

Example 24 (74)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-butoxy benzenesulphonamide.

HPLC retention time (minutes) = 4.44.

Mass data = 494, 492 $(M+H)^+$.

Example 24 (75)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(5-chloro-1,2,4-thiadiazol-3-yl)-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.35.

Mass data = 548, 546, 544 $(M+H)^+$, 317, 214, IS8.

Example 24 (76)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-tert-butylbenzene sulfonamide.

HPLC retention time (minutes) = 4.41.

Mass data = 478, 476 $(M+H)^+$.

Example 24 (77)

5-({[3-(benzyloxy)-5-bromo-2-pyrazinyl] amino) sulfonyl)-4-methyl-2-thiophene carboxylate methyl ester.

HPLC retention time (minutes) = 4.13.

Mass data = 500, 498 $(M+H)^+$, 214.

Example 24 (78)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(5-isoxazolyl)-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.08.

Mass data = 495, 493 $(M+H)^+$, 214.

Example 24 (79)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,3,4,5,6-pentamethylbenzene sulfonamide.

HPLC retention time (minutes) = 4.50.

Mass data = 492, 490 $(M+H)^+$.

Example 24 (80)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(2-(methylthio)-4-pyrimidinyl]-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.24.

Mass data =552, 550 $(M+H)^+$, 214, 158.

Example 24 (81)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-(methylsulfonyl) benzenesulphonamide.

HPLC retention time (minutes) = 3.86.

Mass data = 500, 498 $(M+H)^+$.

Example 24 (82)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-methoxy-2,3,6-trimethyl benzenesulphonamide.

HPLC retention time (minutes) = 4.39.

Mass data = 494, 492 $(M+H)^+$.

Example 24 (83)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-6-(dimethylamino)-2-naphthalenesulfonamide.

HPLC retention time (minutes) = 4.17.

Mass data =515, 513 $(M+H)^+$.

Example 24 (84)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-(2-methoxyphenoxy) benzenesulphonamide.

HPLC retention time (minutes) = 4.28.

Mass data = 544, 542 $(M+H)^+$.

Example 24 (85)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2-methoxy-5-methylbenzene sulfonamide.

HPLC retention time (minutes) = 4.12.

Mass data = 466, 464 $(M+H)^+$.

Example 24 (86)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3, 4-dimethoxybenzene sulfonamide.

HPLC retention time (minutes) = 3.97.

Mass data = 482, 480 $(M+H)^+$.

Example 24 (87)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2, 5-dimethoxybenzene sulfonamide.

HPLC retention time (minutes) = 4.02.

Mass data = 482, 480 $(M+H)^+$.

Example 24 (88)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(2-pyridinyl)-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.08.

Mass data = 505, 503 $(M+H)^+$, 317, 214.

Example 24 (89)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonamide.

HPLC retention time (minutes) = 3.93.

Mass data = 476, 474, 472 $(M+H)^+$, 317, 214.

Example 24 (90)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(3-isoxazolyl)-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.06.

Mass data = 495, 493 $(M+H)^+$, 214.

Example 24 (91)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-6-chloro imidazo [2,1-b][1,3] thiazole-5-sulfonamide.

HPLC retention time (minutes) = 4.04.

Mass data = 504, 502, 500 $(M+H)^+$, 317, 214.

Example 24 (92)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(2-methyl-1,3-thiazol-4-yl)-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.17.

Mass data = 525, 523 $(M+H)^+$, 214.

Example 24 (93)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-methyl-1-phenyl-1H-pyrazole-4-sulfonamide.

HPLC retention time (minutes) = 4.10.

Mass data = 502, 500 $(M+H)^+$, 214.

Example 24 (94)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-(1,3-oxazol-5-yl)-2-thiophene sulfonamide.

HPLC retention time (minutes) = 3.95.

Mass data = 495, 493 $(M+H)^+$, 386, 384, 214.

Example 24 (95)

4-({[3-(benzyloxy)-5-bromo-2-pyrazinyl] amino} sulfonyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester.

HPLC retention time (minutes) = 4.06.

Mass data = 511, 509 $(M+H)^+$, 416, 414, 231, 214.

Example 24 (96)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,4-dimethyl-1,3-thiazole-5-sulfonamide.

HPLC retention time (minutes) = 3.95.

Mass data = 457, 455 $(M+H)^+$, 214.

Example 24 (97)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3,5-dichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.41.

Mass data = 492, 490, 488 $(M+H)^+$, 372, 370, 279, 214, 158.

Example 24 (98)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3,4-dichlorobenzene sulfonamide.

HPLC retention time (minutes) = 4.37.

Mass data = 492, 490, 488 $(M+H)^+$, 317, 214, 158.

Example 24 (99)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-chloro-4-fluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.22.

Mass data = 476, 474, 472 $(M+H)^+$, 317, 214.

Example 24 (100)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-fluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.11.

Mass data = 440, 438 $(M+H)^+$, 279, 214.

Example 24 (101)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3,4-difluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.13.

Mass data = 458, 456 $(M+H)^+$, 317, 214.

Example 24 (102)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-2,3,4,5,6-pentafluorobenzene sulfonamide.

HPLC retention time (minutes) = 4.21.

Mass data =512, 510 $(M+H)^+$, 317, 214.

Example 24 (103)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-methoxy-3,5-dinitrobenzene sulfonamide.

HPLC retention time (minutes) = 4.17.

Mass data = 542, 540 $(M+H)^+$, 317, 214.

Example 24 (104)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-propyl benzene sulfonamide.

HPLC retention time (minutes) = 4.37.

Mass data = 464, 462 $(M+H)^+$, 279, 214.

Example 24 (105)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-butylbenzene sulfonamide.

HPLC retention time (minutes) = 4.43.

Mass data = 478, 476 $(M+H)^+$, 317, 214.

Example 24 (106)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-4-isopropoxy benzenesulphonamide.

HPLC retention time (minutes) = 4.24.

Mass data = 480, 478 $(M+H)^+$, 214.

Example 24 (107)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-(difluoromethoxy) benzenesulphonamide.

HPLC retention time (minutes) = 4.11.

Mass data = 488, 486 $(M+H)^+$, 214.

Example 24 (108)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3,5-bis (trifluoromethyl) benzenesulphonamide.

HPLC retention time (minutes) = 4.37.

Mass data =558, 556 $(M+H)^+$, 317, 214, 158.

Example 24 (109)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-bromo-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.22.

Mass data = 508, 506, 504 $(M+H)^+$, 317, 214, 158.

Example 24 (110)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-5-chloro-2-thiophene sulfonamide.

HPLC retention time (minutes) = 4.24.

Mass data = 464, 462, 460 $(M+H)^+$, 317, 214, 158.

Example 24 (111)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3, 5-dimethyl-4-isoxazole sulfonamide.

HPLC retention time (minutes) = 4.06.

Mass data = 441, 439 $(M+H)^+$, 317, 214.

Example 24 (112)

4-({[3-(benzyloxy)-5-bromo-2-pyrazinyl] amino) sulfonyl)-5-(4-chlorophenyl)-2-methyl-3-furancarboxylate ethyl ester.

HPLC retention time (minutes) = 4.63.

Mass data = 610, 608, 606 $(M+H)^+$, 214.

Example 24 (113)

5-({[3-(benzyloxy)-5-bromo-2-pyrazinyl] amino) sulfonyl)-2-methyl-3-furancarboxylate methyl ester.

HPLC retention time (minutes) = 4.06.

Mass data = 484, 482 $(M+H)^+$, 317, 214.

Example 24 (114)

N-[3-(benzyloxy)-5-bromo-2-pyrazinyl]-3-thiophene sulfonamide.

HPLC retention time (minutes) = 3.99.

Mass data = 428, 426 $(M+H)^+$, 214.

[Biological Examples]

The facts that the compounds of this invention represented by general formula (1) had CCR$ antagonism, inhibited the function of effector cells, had TNF alpha control action and also showed effectiveness in the disease model using animals, were demonstrated for example by the follwoing experiments.

Whole operation was based on fundamental biological techniques, and conventionally used processed were used. Moreover, in the measurement methods of this invention, improvement of measurement precision and/or increase of measurement sensitivity was applied as follows in order to evaluate the compounds of this invention. Below detailed experiment processes were shown.

Biological Example 1. Action with respect to MDC stimulation Ca ion rise.

1-1: Isolation of human CCR4 gene.

Human bone marrow cell cDNA was produced using Marathon cDNA amplification kit (Clontech). The PCR primers, hCCR4XbaI-F1 (sequence number 1) and hCCR4Xba1-R1 (sequence number 2) were designed on the basis of the sequence of GenBankX85740.

Human bone marrow cell cDNA was used as a template, and using Ex Taq (Takara), PCR reaction (2 minutes at 95°C, to [30 secs at 95°C, 45 secs at 60°C, 1 minute at 72°C] x 35 times) was carried out. Amplified PCR product was subjected to 1 % agarose gel electrophoresis, thereafter purified using QIAquick Gel Extraction Kit (QIAGEN) and it was cleaved with restriction enzyme XbaI. Cleaved fragment was connected with expression vector pEF-BOS-bsr (Nucleic Acid Research, 1990, Vol. 18, no. 17, p.5322) using DNA Ligation Kit Ver, 2 (Takara), and Escherichia coli DH5a was transformed. This plasmid pEF-BOS-bsr/hCCR4 was prepared, and DNA sequence was confirmed.

1-2: Cultivation of CHO cell.

CHO-dhfr(-) was cultured using Ham's F-12 (containing fetal bovine serum (10 %), penicillin (100 U/mL), streptomycin (100 mg/mL)). Moreover, the transformed cells were cultured by addition of blasticidin (5 mg/ mL) to the above.

1-3: Transformation into CHO cell.

Using DMRIE-C reagent (Gibco BRL), transduction was of plasmid pEF-BOS-bsr/hCCR4 into CHO-dhfr(-) cells was carried out. 48 hours later, and it was changed to the culture medium containing 5 mg/mL blasticidin, and selection was carried out, and stable overexpression cells were established.

1-4: Inhibition experiment with respect to MDC action via CCR4 (Ca ion transient rise induction activity of MDC).

Established human CCR4 stable overexpression CHO cell (CCR4/CHO cell) was suspended in Ham's F-12 culture medium and FBS (10%) and plated on 96-well plate by 3.0 x 10^4 cells/well. It was cultured for 1 day at 37°C, thereafter, culture supernatant was eliminated, and Ham's F-12 culture medium (containing Fura-2AM (5 μM), probenecid (2.5 mM) and HEPES (20 mM; pH 7.4)) was added by 80 ml/well and was incubated at 37°C under kight-shielding condition for one hour. It was washed twice with 1 x Hanks/HEPES (20 mM, pH7.4) solution, thereafter, the same solution was added by 100 ml/well. With respect to these CCR4/CHO cells which took in Fura-2AM, when 3 minutes was passed after the addition of test compound, the recombinant human MDC (PeproTech) diluted with 1 x Hanks/HEPES (20 mM, pH7.4) solution was added by the final concentration of 10 nM. The transient rise of Ca2+ concentration in the cells which was

induced by human MDC was measured using Ca2+ detector for 96 well (Hamamatsu Photonics), and the inhibition rate of test compound (%) was calculated using the following caculation formula.

Inhibition rate = [(Ec - Ba) / Ec] x 100.

Ec = The measured value of Ca2+ transient rise due to MDC.
Ea = The measured value of Ca2+ transient rise due to MDC when the test compound was added.

The inhibition ratio was calculated for compound at each concentration, and the value (IC50 value) which 50 % showed inhibition ratio was determined from the inhibition curve.

As a result, the compounds of this invention showed inhibition of 50% or more at 10 μM. For example, the IC50 value was 0.13 μM for the compound of Example 1 (1), and the IC50 value was 0.016 μM for the compound of Example 1 (2).

Biological Example 2. Action with respect to MDC stimulated cell migration.

2-1: Inhibition test with respect to MDC-induced T cell strain (CCRF-CEM cell) migration

Culture medium (0.3 mL) either containing or not containing MDC (20 nM, PeproTech) was added to the lower chamber of 24-well trans well plate, and furhtermore, culture medium (0.3 mL) containing of 2 times concentration of test drug solution (including 0.02 % DMSO) or a culture medium (0.3 mL) only containing DMSO was added. CCRF-CEM cell suspension (0.05 mL) prepared to $1x10^6$ cells/50 μL and 2 times concentration of test drug solution (0.05 mL) were added to the upper chamber, and the test was started by superimposing the upper chamber tothe lower chamber. It was cultured in a carbon dioxide incubator (5 % CO2, humidity 95 %) at 37°C for four hours and the cells which remained in the upper chamber was eliminated by suction. A 0.1 mL buffer (ethylene diamine tetraacetic acid sodium salt (EDTA) (20 μM) containing phosphate-buffered physiological saline (PBS)) was added, and it was reacted at 4°C for 30 minutes. The trans well plate was centrifuged for five minutes (1000 r.p.m), and the culture medium of the lower chamber (600 μL) was recovered, and the number of cells were counted using flow site meter (Bekton Dickenson).

Migration inhibiting activity by the compounds of this invention was calculated as inhibition ratio (%) according to following equation, wherein the value of the well to which DMSO-containing culture medium which did not include the test drug was assumed control value (A), and the value of the well to which DMSO-containing culture medium which included the test drug was

assumed as (B).

Inhibition ratio (%) = [(A-B) / A] x 100.

Inhibition ratio was calculated at each concentration of the compound, and the value (IC50 value) which showed inhibition ratio of 50 % was determined from the inhibition curve.

As a result, the compounds of this invention showed inhibition of 50% or more at 10 μM. For example, the compound of Example 6 (1) had IC50 value of 0.01 μM.

Biological Example 3. Mouse asthma model.

3-1: mouse OVA-induced asthma model.

Ovalbumin (OVA, 0.2 mg/mL) and Alum (8 mg/mL) which were prepared with physiological saline were intraperitoneally administered (500ml) to mice (male C57BL/6) on the test start day (Dayl) and one week later thereof (Day8) , and it was sensitised. Mice were placed in inhalation chamber (W: 240 mm x L: 240 mm x H: 120mm), on Day 15-21and, using ultrasonic nebulizer (NE-U12, Omron), it was induced by spraying 2 % OVA solution for 20 minutes. The compounds of this invention were suspended in a vehicle, and it was administered orally 30 minutes before the OVA sensitization of Day 8 and 30 minutes before the OVA induction on Day 15-21. Only the vehicle was administered to the control group. On Day 21, after 3 hours from the OVA inhalation, mice were bled to death, and catheter tube was intubated from the trachea, and bronchoalveolar lavage fluid (BALF) was obtained by washing the lung with heparin sodium-containing physiological saline (10 U/mL). The number of leukocyte in BALF was counted using hemocyte counter (SF-3000, Sysmex).

As a result, the compounds of this invention, for example the compound of Example 1 (3) inhibited invasion of leukocyte to lung at a dose of 30 mg/kg.

Biological Example 4: mouse dermatitis model.

4-1: Mouse DTH model.

The abdomen of mice (male Balb/c) was shaved with a hair clipper, and 7 % (w/v) 2,4,6-trinitro chlorobenzene (TNCB) ethanol solution (100 mL) was applied to the abdomen, and sensitization was carried out. On 7 days after sensitisation, 1 % (w/v) TNCB olive oil solution (20 μL), was applied to mouse auricle (both sides of the right ear) and the induction was carried out. The compounds of this invention were dissolved in a vehicle, and were applied (20 μL) to mouse auricle (both sides of the right ear) 2 hours before TNCB application. Only the vehicle was

applied to the control group. The mouse auricle thickness was measured just before compound application and 24 hours after TNCB application using Dial thickness gauge (Ozaki Factories) and this was used as the indicator of the effectiveness in the mouse DTH model.

As a result, the compounds of this invention, for example the compound of Example 6 (1) inhibited swelling of auricle at concentration of 5 %.

4-2: Mouse hapten successive application dermatitis model.

1 % (w/v) TNCB solution (acetone : olive oil = 4:1) (20 μL) was applied to auricle (both sides of the right ear) of mice (male Balb/c), and the initial sensitization was carried out. 1 % (w/v) TNCB solution (acetone : olive oil = 4:1) (20 μL) was applied to mice auricle on 7 days after the sensitization, and induction was carried out (Day 0). In Day 2, 4, 6, 8, 10, 12, 14, 16, the same operation as in Day 0 was repeated furthermore. The compounds of this invention were dissolved in a vehicle, and were applied (20 μL) to mouse auricle (both sides of the right ear) 2 hours before TNCB application. Only the vehicle was applied to the control group. The mouse auricle thickness was measured just before compound application and 24 hours after TNCB application using Dial thickness gauge (Ozaki Factories) and this was used as the indicator of the effectiveness in the mouse hapten successive application dermatitis model.

As a result, the compounds of this invention, for example the compound of Example 1 (3) inhibited swelling of auricle at concentration of 5 %.

Biological Example 5: mouse TNF alpha production model.

5-1: Mouse LPS stimulation TNF alpha production model.

The compounds of this invention suspended in a vehicle were orally administered to mice (male C57BL/6), and 30 minutes later, lipopolysaccharide (LPS, 055:B5, Sigma) was administered intraperitoneally with a dose of 60 mg/kg. Only the vehicle was administered orally to the control group. On 60 minutes after the LPS treatment, heparin added blood sampling was carried out from the abdomenal vena cava under ether anaesthesia, and plasma was obtained by performing centrifugation (12000 r.p.m) at 4°C for three minutes. The obtained plasma sample was stored at 80°C until time of use. TNF alpha in plasma was determined using ELISA kit (R&D systems) .

As a result, the compounds of this invention, for example the compound of Example 1 (1) inhibited the quantity of TNF alpha production by LPS stimulation at a dose of 100 mg/kg.

Preparation Example 1

Each of the following components was mixed in accordance with conventional procedures, thereafter it was tabletted, and 100 tablets containing 50 mg active ingredient per tablet were obtained.

• 6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine	5.0 g
• Carboxymethylcellulose calcium (disintegrating agent)	0. 2 g
• Magnesium stearate (lubricant)	0.1 g
• Microcrystalline cellulose	4.7 g.

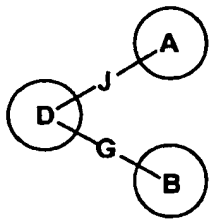
Preparation Example 2

Each of the following components was mixed in accordance with conventional procedures, thereafter the solution was sterilized in accordance with conventional procedures, it was packed into ampule by 5 mL, it was freeze-dried in accordance with conventional procedures, and 100 ampules which contained 20 mg active ingredient per ampule were obtained.

• 6-bromo-2-((3,4-dimethoxyphenyl) methyl oxy)-3-(4-methylphenyl sulfonyl amino) pyrazine	2.0g
• Mannitol	20 g
• Distilled water	500 ml

Patnet Claims

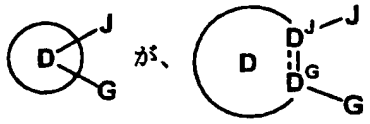
1. A compound or salts thereof represented by general formula (I)



(I)

(in the formula ring A, ring B and ring D each independently denote optionally substituted cyclic group, and J denotes a bond or a spacer having the number of main chain atoms of 1-8, and G represents a bond or a spacer having the number of main chain atoms of 1-4).

2. A compound in accordance with aforesaid Claim 1, wherein



is

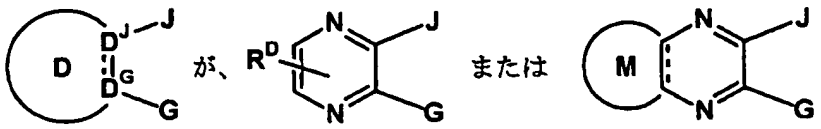
(wherein, DJ and DG each independently denote carbon atom or nitrogen atom,
---- denotes single bond or double bond, and
when ---- denotes double bond, DJ and DG represent carbon atom).

3. A compound in accordance with aforesaid Claim 2, wherein the ring D is an optionally substituted carbocyclic ring.

4. A compound in accordance with aforesaid Claim 2, wherein the ring D is an optionally substituted heterocyclic ring.

5. A compound in accordance with aforesaid Claim 4, wherein the heterocyclic ring is 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms.

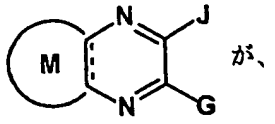
6. A compound in accordance with aforesaid Claim 2, wherein



is or

(wherein, RD denotes substituent of ring D, and M represents 3-11-membered optionally substituted monocyclic or bicyclic group).

7. A compound in accordance with aforesaid Claim 6, wherein



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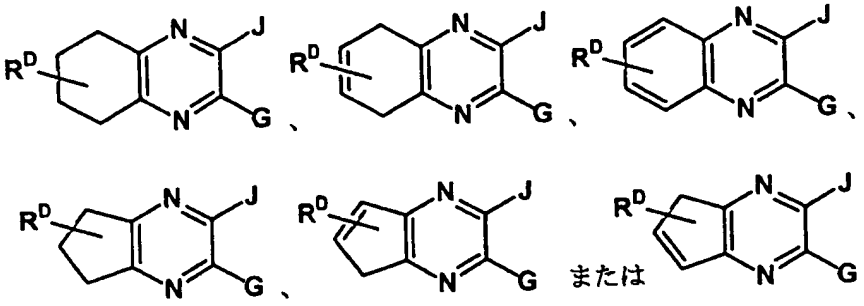

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または

or

(wherein, RD has the same said meaning as described in aforesaid 6).

8. A compound in accordance with aforesaid Claim 1, wherein the ring A is an optionally substituted carbocyclic ring.

9. A compound in accordance with aforesaid Claim 1, wherein the ring A is an optionally substituted heterocyclic ring.

10. A compound in accordance with aforesaid Claim 8, wherein the carbocyclic ring is C3-15 mono-, di- or tri-cyclic carbocyclic ring.

11. A compound in accordance with aforesaid Claim 9, wherein the heterocyclic ring is 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms.

12. A compound in accordance with aforesaid Claim 10, wherein the carbocyclic ring is benzene ring or naphthalene ring.

13. A compound in accordance with aforesaid Claim 11, wherein the heterocycle is pyridine ring, pyrazole ring, dioxan indan ring or benzodioxan ring.

14. A compound in accordance with aforesaid Claim 1, wherein the ring B is an optionally substituted carbocyclic ring.

15. A compound in accordance with aforesaid Claim 1, wherein the ring B is an optionally substituted heterocyclic ring.

16. A compound in accordance with aforesaid Claim 14, wherein the carbocyclic ring is C3-15 mono-, di- or tri-cyclic carbocyclic ring.

17. A compound in accordance with aforesaid Claim 15, wherein the heterocyclic ring is mono-, di- or tri-cyclic heterocycle of 3-15-membered containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom.

18. A compound in accordance with aforesaid Claim 16, wherein the carbocyclic ring is C3-8monocyclic carbocyclic ring.

19. A compound in accordance with aforesaid Claim 17, wherein the heterocyclic ring is 3-8-membered monocyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom.

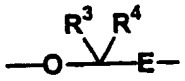
20. A compound in accordance with aforesaid Claim 18, wherein the carbocyclic ring is benzene ring.

21. A compound in accordance with aforesaid Claim 19, wherein the heterocyclic ring is pyridine ring or thiophene ring.

22. A compound in accordance with aforesaid Claim 1, wherein J is a spacer having the number of main chain atoms of 1-8 containing at least one oxygen atom.

23. A compound in accordance with aforesaid Claim 22, wherein the oxygen atom is bonded to ring D.

24. A compound in accordance with aforesaid Claim 22, wherein J is



(in this group, R3 and R4 each independently denote hydrogen atom or C1-8 alkyl group, and E represents bond or a spacer having the number of main chain atoms of 1-6).

25. A compound in accordance with aforesaid Claim 24, wherein R3 and R4 each independently represent hydrogen atom or methyl group..

26. A compound in accordance with aforesaid Claim 24, wherein E is a bond.

27. A compound in accordance with aforesaid Claim 24, wherein E is a spacer having the number of main chain atoms of 1-6.

28. A compound in accordance with aforesaid Claim 27, wherein E is C1-4 alkylene group or C1-3 alkylene oxy group.

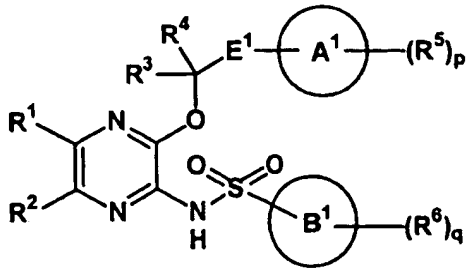
29. A compound in accordance with aforesaid Claim 28, wherein E is methylene group or methylene oxy group.

30. A compound in accordance with aforesaid Claim 1, wherein G is a spacer having the number of main chain atoms of 1-4 containing at least one nitrogen atom.

31. A compound in accordance with aforesaid Claim 30, wherein G is -NRT1-, -NRT1-SO2-, -NRT1-CO-, -NRT1-CO-NRT2-, -NRT1-SO2-NRT2-, -NRT1-COO-, NRT1-O-, -NRT1-NRT2-, -NRT1-W-, -SO2-NRT1-, -CO-NRT1-, -OCO-NRT1-, -CO-NRT1- or -W-NRT1- (in the groups, W denotes an optionally substituted divalent aliphatic hydrocarbon group of carbon number 1-3, and RTI and RT2 each independently represent hydrogen atom, optionally substituted C1-8 alkyl group, optionally substituted C2-8 alkenyl group, optionally substituted C2-8 alkynyl group or optionally substituted 3-8-membered cyclic group).

32. A compound in accordance with aforesaid Claim 31, wherein G is -NH-SO2-.

33. A compound in accordance with aforesaid Claim 1, wherein the compound is general formula (A)



(A)

(in the formula, R1 and R2 each independently represent (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) halogen atom, (6) cyano group, (7) nitro group, (8) -CONR7R8, (9) -COOR9, (10) Cyc1 or (11) C1-8 alkyl group substituted by 1-5 groups arbitrarily selected from (a) -CONR7R8, (b) -COOR9, (c) -OR10, (d) -NR11R12, (e) halogen atom and (f) Cyc1, or

R1 and R2 may be linked together to forn C3-4 alkylene group, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH_2-CH_2- are denoted. Wherein the formed carbon ring may be substituted by C1-8 alkyl group, C2-8 alkenyl group, C2-8 alkynyl group, C1-8 alkoxy group, halogen atom, cyano group, nitro group, hydroxy group (in this group, R7 and R8 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc2, (6) -OR13, (7) C1-8 alkyl group C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 groups arbitrarily selected from (a) -OR13, (b) -NR14R15, (c) -NR16COR17, (d) halogen atom, (e) CF3 and (f) Cyc2, or

R7 and R8 may be linked together with the nitrogen atom that they are bonded to forn a 3-8-membered monocyclic heterocycle containing at least 1 nitrogen atom and also containing as other heteroatoms 0-3 nitrogen atoms, 0-1 oxygen atom and/or 0-1 sulfur atom. Wherein aforesaid heterocycle may be substituted by C1-8 alkyl group substituted by (a) C1-8 alkyl group, (b) halogen atom, (c) hydroxy group or (d) hydroxy group,

R13-R17 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc1 or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by Cyc1,

R9-R12 each independently denote (1) hydrogen atom (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group (5) Cyc1 or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by Cyc1,

Cyc1 denotes mono-, di- or tri-cyclic carbocyclic of C3-15 or 3-15-membered mono-, di- or tri-cyclic heterocycle of containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as or heteroatoms. Wherein Cyc1 may be substituted by 1-5 species of R18,

R18 denotes (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) trifluoromethyl group, (8) trifluoromethoxy group (9) -OR19, (10) -SR20, (11) -NR21R22, (12) -COR23, (13) -COOR24, (14) -NR25COR26, (15)-

CONR27R28, (16) Cyc2 or (17) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by1-5 groups arbitrarily selected from (a) halogen atom, (b) cyano group, (c) nitro group, (d) trifluoromethyl group, (e) trifluoromethoxy group (f) -OR19, (g) -SR20, (h) -NR21R22, (I) -COR23, (j) -COOR24, (k) -NR25COR26, (l) -CONR27R28 and (m) Cyc2,

R19-R28 each independentlydenote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc2, or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by Cyc2,

Cyc2 denotes monocyclic carbocyclic of C3-8 or 3-8-membered monocyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms. Wherein Cyc2 may be substituted by 1-5 species of R29, and

R29 denotes (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) hydroxy group, (8) trifluoromethyl group, (9) trifluoromethoxy group or (10) -OR100, and

R100 represents C1-8 alkyl group),

R3 and R4 each independently denote hydrogen atom or C1-8 alkyl group,

E1 denotes a bond or C1-6 alkylene group. Wherein the carbon atoms of said alkylene group may be substituted by oxygen atom, sulfur atom or NR30-,

R30 denotes (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) phenyl group, or (5) C1-8 alkyl group substituted by phenyl group,

ring A1 denotes mono-, di- or tri-cyclic carbocyclic of C3-15 or 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms,

R5 denotes (1) C1-8 alkyl group (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) trifluoromethyl group, (8) trifluoromethoxy group, (9) -OR31, (10) -NR32R33, (11) -NR34COR35, (12) Cyc3 or (13) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 groups arbitrarily selected from (a) halogen atom, (b) cyano group, (c) nitro group, (d) trifluoromethyl group, (e) trifluoromethoxy group, (f) -OR31, (g) -NR32R33, (h) -NR34COR35, and (i) Cyc3,

R31-R35 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) C2-8 alkenyl group, (4) C2-8 alkynyl group, (5) Cyc3 or (6) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 groups arbitrarily selected from (a) Cyc3, (b) -OR36 and (c) -NR37R38,

R36-R38 each independently denotes (1) hydrogen atom, (2) C1-8 alkyl group, (3) -OR39 or (4) -NR40R41,

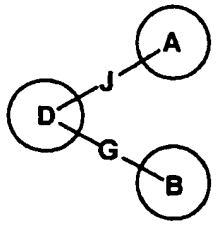
R39-R41 each independently denotes a hydrogen atom or C1-8 alkyl group,

Cyc3 denotes monocyclic carbocyclic of C3-8 or 3-8-membered monocyclic heterocycle

containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatom,
ring B1 denotes mono-, di- or tri-cyclic carbocyclic of C3-15 or 3-15-membered mono-, di- or tri-cyclic heterocycle containing 1-4 nitrogen atoms, 1-2 oxygen atoms and/or 1-2 sulfur atoms as heteroatoms,
R6 is (1) C1-8 alkyl group, (2) C2-8 alkenyl group, (3) C2-8 alkynyl group, (4) halogen atom, (5) cyano group, (6) nitro group, (7) trifluoromethyl group, (8) trifluoromethoxy group, (9) -OR42, (10) -NR43R44, (11) -SR101, (12) -SO2R102, (13) -COR103, (14) -COOR104, (15) Cyc2 or (16) C1-8 alkyl group, C2-8 alkenyl group or C2-8 alkynyl group substituted by 1-5 group arbitrarily selected from (a) -COOR104, (b) -NR105COR106 and (c) Cyc2,
R42-R44, R101-R106 each independently denote (1) hydrogen atom, (2) C1-8 alkyl group, (3) Cyc2, (4) -COR 107 or (5) C1-8 alkyl group substituted by 1-5 halogen atoms,
R107 denotes C1-8 alkyl group, and
p and q each independently denote 0 or an integer of 1-5.].

34. A prodrug of compound in accordance with aforesaid Claim 1.

35. A medicinal composition which is obtained by containing the compounds or salts thereof represented by general formula (I)



(I)

(in the formula ring A, ring B and ring D each independently denote optionally substituted cyclic group, and J denotes a bond or a spacer having the number of main chain atoms of 1-8, and G represents a bond or a spacer having the number of main chain atoms of 1-4).

36. A medicinal composition in accordance with aforesaid Claim 35 that is a chemokine receptor antagonist.

37. A medicinal composition in accordance with aforesaid Claim 36, wherein the chemokine receptor is CCR4.

38. A medicinal composition in accordance with aforesaid Claim 37 that is a prevention and/or therapeutic agent of CCR4-mediated disease.

39. A medicinal composition in accordance with aforesaid Claim 38, wherein the CCR4-mediated disease is inflammation / allergic disease, metabolism / endocrine system disease, cancerous disease or infection.

40. A medicinal composition in accordance with aforesaid Claim 39, wherein the CCR4-mediated disease is inflammation / allergic disease.

41. A medicinal composition in accordance with aforesaid Claim 40, wherein the inflammation / allergic disease is respiratory system disease or dermatosis.

42. A medicinal composition in accordance with aforesaid Claim 41, wherein the respiratory system disease is asthma.

43. A medicinal composition in accordance with aforesaid Claim 41, wherein the dermatosis is atopic dermatitis.

44. A prevention and/or therapy method of CCR4-mediated disease in mammalian organisms characterised in that an effective dose of compounds or salts thereof in accordance with aforesaid Claim 1 is administered to mammalian organism.

45. Use of compounds or salts thereof in accordance with aforesaid Claim 1 to produce prevention and/or therapeutic agent of CCR4-mediated disease.

46. A medicinal composition formed from a prevention and/or therapeutic agent of CCR4-mediated disease containing compounds or salts thereof in accordance with aforesaid Claim 1 as effective component, and one or more drugs selected from bronchodilator, steroid drug, non-steroid anti-inflammatory agent, leukotriene receptor antagonist, phosphodiesterase inhibitor, immunosuppressive drug, antiallergic drug, mediator releaser suppressant antihistamine, metabolism promotion agent and/or chemokine inhibitor.

47. A medicinal composition in accordance with aforesaid Claim 35 that is a function inhibitor of effector cell.

48. A medicinal composition in accordance with aforesaid Claim 47 that is a cell migration function inhibitor.

49. A medicinal compositions in accordance with aforesaid Claim 35 that is TNF alpha controlling agent.

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